Steric and Electronic Effects on ^{15}N Chemical Shifts of Piperidine and Decahydroquinoline Hydrochlorides[1]

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Abstract: Natural-abundance ^{15}N NMR chemical shifts of a number of closely related *C*- and *N*-methyl-substituted piperidine and decahydroquinoline hydrochlorides have been measured in chloroform and methanol. For each solvent, the ^{15}N shifts of the salts of secondary and tertiary amines give different linear correlations with the ^{13}C shifts of the corresponding carbons of their hydrocarbon analogues. Additive shift parameters as well as protonation-shift parameters for carbon substitution near nitrogen have been determined. Three of the nine parameters have a pronounced solvent dependence. The substituent-shift parameters for hydrochlorides are in general closer to the analogous values for ^{13}C NMR than the corresponding parameters which correlate the ^{15}N shifts of the free amines. The parameters for substitution on β carbons are an exception. The ^{13}C shifts of some of the compounds can be used to elucidate conformational questions.

I. Introduction

In an earlier paper on the natural-abundance ^{15}N spectra of piperidines and related compounds, it was shown that the nitrogen chemical shifts could be correlated with a set of additive substituent parameters.[2] Some of these parameters showed significant solvent dependences. Plots of the ^{15}N shifts measured in the same solvent vs. the ^{13}C shifts of ring carbons located in the same place as the nitrogens in corresponding cyclohexane compounds were quite linear for all the secondary amines and for two separate groups of *N*-methyl derivatives. The few tertiary amines which showed large deviations from the $^{15}N/^{13}C$ shift-correlation line had the common structural feature of carbon–carbon bonds oriented antiperiplanar to the nitrogen lone pair. The large shift effect connected with this stereoelectric arrangement was used to estimate the axial/equatorial equilibrium of *N*-methylpiperidine.

The present study concerns the ^{15}N chemical shifts of the hydrochlorides of amines. If these shifts could be correlated with additive substituent parameters, further information on the structures of saturated amines might be derived by measuring the changes in shift produced by protonation. Still further insight might be gained from comparison of the $^{15}N/^{13}C$ shift correlations of the amines[2] and the amine salts with the ^{13}C shifts of cyclohexanes, because effects due to the size or delocalization of the lone pair either should be expected to disappear or become smaller by protonation. It was also of interest to determine the possible influences of the positive charge and shift effects due to the solvent, concentration of solute, and the counterion.

II. Experimental Section

Nitrogen-15 chemical shifts were determined with a Bruker WH-180 FT NMR spectrometer operating at 18.25 MHz. The concentrations of the amine hydrochloride solutions were 9 ± 1 mol % in chloroform, 4.5 ± 0.5 mol % in absolute methanol, and 7.5 ± 0.5 mol % in a mixture of 82 mol % chloroform and 18 mol % methanol. The shifts are reported in parts per million upfield from external ^{15}N-enriched 1 M nitric acid in D_2O. The values which are accurate to about 0.2 ppm are not corrected for bulk susceptibility effects. The reference was made by dilution of 44% $H^{15}NO_3$ (99 atom %) with D_2O to 1 M. The reproducibility of the shift of such solutions is within 0.15 ppm. All shifts of this study are measured with identical references. The bulk susceptibility, K^{ν}, of 1 M nitric acid is $-0.715 \pm 0.005 \times 10^{-6}$. The shift of 1 M nitric acid not corrected for bulk susceptibility is 6.2 ppm upfield from neat nitromethane, 298.7 ppm downfield from urea (2 M in H_2O), 332.8 ppm downfield from tetramethylammonium chloride (2 M in H_2O), and 355.0 ppm downfield from the ammonium resonance of ammonium nitrate (2 M in H_2O).

For a reasonable signal-to-noise ratio, it was necessary to accumulate 500–1000 pulses (25°/20 μs) with repetition rates between 2 and 5 s. In some cases, much longer accumulation times (up to 21 h) were needed to detect the signals of amine salt epimers present in low concentration. The base-catalyzed nitrogen epimerization was found to be slow enough in both solvents to observe separate sharp signals for diastereomeric salts. The proton-noise decoupling of hydrochloride solutions turned out to be rather difficult, because a high portion of the decoupling power is reflected when the dielectric constant of the sample is increased. Efficient decoupling of both the deshielded ammonium protons and the protons on α carbons was therefore not always possible. The resulting broadening of the signals (up to 20 Hz) in some instances precluded the observation of isomers with low concentrations. Because of the high decoupling power needed (5 W), the sample was kept near ambient temperatures by blowing cold nitrogen (0 °C) through the probe.

Peak assignments for mixtures of isomers were made by utilizing the intensity ratios of the signals or, when these were close to 1:1, by comparison with the spectrum of one pure isomer.

^{13}C NMR spectra were measured of chloroform solutions with a Varian XL-100 spectrometer, and proton spectra on a Varian A-60A instrument.

The crystalline hydrochlorides were prepared by passing dry hydrogen chloride into solutions of the amines in anhydrous ether. The salts were collected by filtration, washed with ether, and dried under reduced pressure. The preparation of the amines was described previously.[2] Mixtures of *N*-methyl-*cis*- and *N*-methyl-*trans*-3,5-dimethylpiperidine (**7b, 8b**), and *N*-methyl-*cis*- and *N*-methyl-*trans*-2,6-dimethylpiperidine (**5b, 6b**), were separated by chromatography on alumina.[3] Better separations were obtained using alumina (neutral, activity 1, Woelm) and eluting first with petroleum ether (bp 35–60 °C) and then with petroleum ether/ether mixtures, increasing the amount of ether in 4 vol % steps, rather than just eluting with ether.

III. Results and Discussion

The ^{15}N chemical shifts of the hydrochlorides of various methylpiperidines, decahydroquinolines, and related compounds measured in chloroform and methanol are given in Table I along with the protonation shifts in methanol. Because some of the secondary salts were not very soluble in chloroform, their ^{15}N shifts were also measured in a mixture of 82 mol % chloroform and 18 mol % methanol. Plots of the ^{15}N shifts vs. the corresponding ^{13}C shifts are shown in Figures 1 ($CHCl_3$), 2 (CH_3OH), and 3 ($CHCl_3/CH_3OH$). In each case, separate linear correlations are found for the secondary and the tertiary salts. The slopes, intercepts, and correlation coefficients of the least-squares lines are listed in Table II. Table III gives the carbon shifts of the corresponding carbons of the analogous cyclohexanes[4] and the deviations on the nitrogen scale from the $^{15}N/^{13}C$-correlation line for both the salts and the free bases[2] measured in different solvents.

It has already been shown that there are quite distinctly

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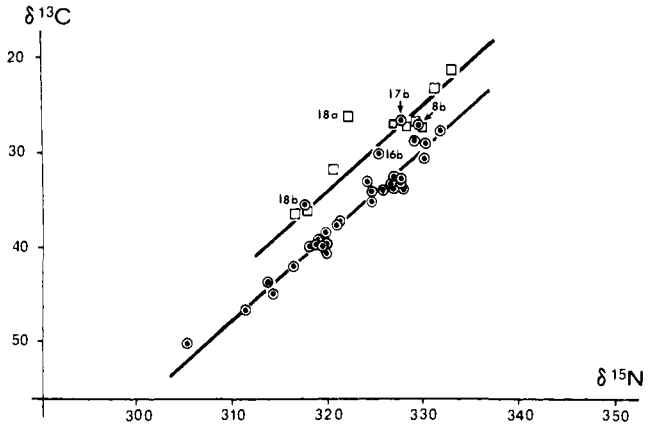


Figure 1. Correlation of $^{15}N/^{13}C$ NMR chemical shifts of secondary amine hydrochlorides, □, and tertiary amine hydrochlorides, ⊙, in chloroform solution.

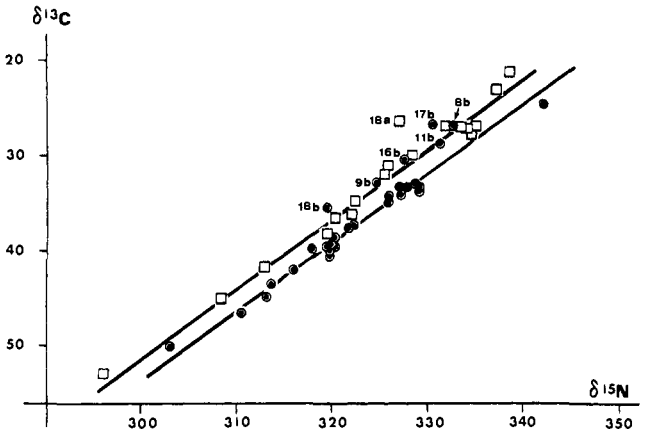


Figure 2. Correlation of $^{15}N/^{13}C$ NMR chemical shifts of secondary amine hydrochlorides, □, and tertiary amine hydrochlorides, ⊙, in methanol solutions.

different intercepts, but similar slopes (for a given solvent), of the $^{15}N/^{13}C$-shift correlations for the secondary and tertiary piperidines themselves, and one possible reason for this could be the nitrogen lone pair which is expected to produce a large contribution to the paramagnetic shift term. Different mean radii for the lone pairs of secondary and tertiary amines would affect the nitrogen shifts through the $1/r^3$ term of the shielding equation.[5,6] If the condition of the lone pairs were the only difference between secondary and tertiary amines, hydrogen bonding or protonation might be expected to diminish the differences between the correlation lines. This is, in fact, observed, and separations between the correlation lines of secondary and tertiary amines (12.5 ppm for a carbon shift of 37 ppm) shrink to 8.5 ppm on going from cyclohexane to methanol as solvent, and are only 5.5 ppm for the hydrochlorides in chloroform and 3.5 ppm for the hydrochlorides in methanol. A very important shift effect, which is evident only for tertiary amines, appears to involve delocalization of the lone pair to antiperiplanar C(α)H bonds.[2] If this effect were absent, the separation of the $^{15}N/^{13}C$ shift correlation lines of secondary and tertiary amines would be much larger than 12.5 ppm, as can be seen from the large deviations of those tertiary amines which are stereochemically constrained or otherwise constructed not to have antiperiplanar protons (see Table III). Protonation cancels the antiperiplanar effect and the ^{15}N shifts of the hydrochlorides of the deviant amines correlate well with the other tertiary salts; examples are *N*,(*trans*-2,6)-trimethylpiperidine (**6b**), *N*,2,2,6,6-pentamethylpiperidine (**13b**), *N*-methyl-2-azaadamantane (**14b**), *N*-isopropylpiperidine (**20**), and quinuclidine (**22**) (Table III).

The influence of protonation on the ^{15}N shifts is the net of cancellation of effects due to the nitrogen lone pair in the amine, and of new effects connected with introduction of positive charge and an additional N–H bond in the salts. The downfield shifts observed on protonation of most of the compounds studied suggest reduced electron shielding with formation of positively charged nitrogen. Some of the positive charge will be expected to be delocalized to the close-by carbons and hydrogens as well. In this connection, CNDO/2 calculations by Morishima and co-workers[7] indicate that, in amine salts, the positive charge formed on nitrogen is spread over the C–H hydrogens, primarily those on the α and β carbons, while the electron densities on the carbon atoms remain constant or even increase. Such a charge redistribution is in qualitative agreement with the observed deshielding of the proton resonances and the shielding of most carbon shifts on protonation of a saturated amine.[7,8] Furthermore, substitution of the C–H hydrogens by carbons is found to reverse the protonation effect on the α carbons from the upfield direction to the downfield direction and also attenuates the large shielding effect of β carbons. Structural effects on the ^{15}N protonation shifts are not wholly consistent with the postulated bond polarizations. Thus, substitution of hydrogens on α carbons by methyl groups decreases the deshielding protonation effect on the ^{15}N resonances and eventually produces a shielding effect, e.g, *cis*-2,6-dimethylpiperidine (**5a**) (Table I). However, increased deshielding on protonation is observed when methyl groups are substituted for hydrogens on β carbons, and this effect is responsible for the rather large deviations from the $^{15}N/^{13}C$ shift correlations observed for hydrochlorides with gauche γ carbons. This effect is more pronounced for the hydrochlorides derived from tertiary amines than for those from secondary amines. Examples include *N*,(*trans*-3,5)-trimethylpiperidine (**8b**), − 4.4 ppm; *N*,3,3-trimethylpiperidine (**11b**), − 3.3 ppm; *N*-methyl-*cis*-decahydroquinoline (**16b**, N-inside isomer), −5.0 ppm; and *N*-methyl-8-(e)-methyl-*trans*-decahydroquinoline (**17b**), − 6.9 ppm (Table III and Figures 1 and 2). The attenuation of the ^{15}N protonation shift by β carbons causes the β parameter for hydrochlorides to be smaller than that for free amines (see below), and is responsible for the fact that the slopes of the $^{15}N/^{13}C$ shift-correlation lines are closer to unity for the salts than for the free bases (Table II). Possible reasons for the protonation shifts of tertiary amines being larger than the protonation shifts of secondary amines were mentioned above in connection with the separation of the correlation lines. Although the ^{15}N chemical shifts

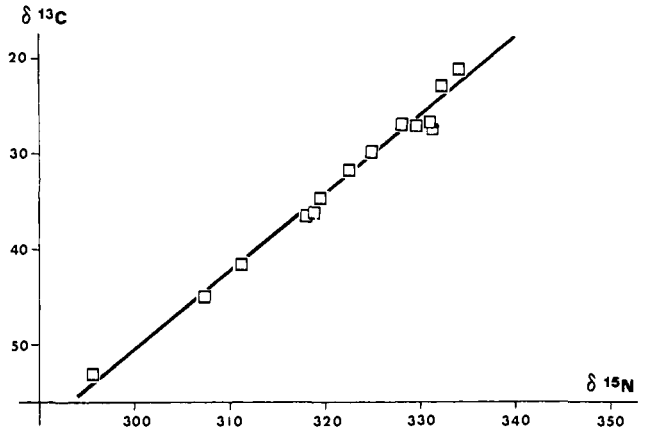


Figure 3. Correlation of $^{15}N/^{13}C$ NMR chemical shifts of secondary amine hydrochlorides in chloroform/methanol (82:18) solution.

Table I. ^{15}N Chemical Shifts of Amine Hydrochlorides

Amine		Solvent[a]	Concn[b]	Isomer[c]	$\delta^{15}N$[d]	$\Delta\delta(H^+)$[e]
Piperidine	**1a**	$CHCl_3/CH_3OH$	7.0		331.3	
		CH_3OH	4.0		344.8	−2.2
2-Methylpiperidine	**2a**	$CHCl_3$	9.2		317.9	
		$CHCl_3/CH_3OH$	8.4		318.8	
		CH_3OH	4.0		322.1	+1.5
3-Methylpiperidine	**3a**	$CHCl_3$	7.7		328.4	
		$CHCl_3/CH_3OH$	7.1		329.8	
		CH_3OH	4.0		333.8	−3.3
4-Methylpiperidine	**4a**	$CHCl_3$	6.5		329.6	
		$CHCl_3/CH_3OH$	7.7		331.2	
		CH_3OH	4.0		335.2	−2.8
cis-2,6-Dimethylpiperidine	**5a**	$CHCl_3/CH_3OH$	7.9		307.3	
		CH_3OH	4.5		308.4	+4.9
trans-2,6-Dimethylpiperidine	**6a**	$CHCl_3/CH_3OH$	7.9		311.3	
		CH_3OH	4.5		313.0	+1.5
cis-3,5-Dimethylpiperidine	**7a**	$CHCl_3$	7.7		327.4	
		$CHCl_3/CH_3OH$	7.3		328.3	
		CH_3OH	4.0		332.1	−4.3
trans-3,5-Dimethylpiperidine	**8a**	$CHCl_3$	7.7		333.1	
		$CHCl_3/CH_3OH$	7.3		334.4	
		CH_3OH	4.0		338.7	−8.7
cis-2,3-Dimethylpiperidine	**9a**	$CHCl_3$	9.3		320.7	
		$CHCl_3/CH_3OH$	8.3		322.5	
		CH_3OH	4.8		325.6	
trans-2,3-Dimethylpiperidine	**10a**	$CHCl_3$	9.3		316.6	
		$CHCl_3/CH_3OH$	8.3		318.2	
		CH_3OH	4.8		320.5	
3,3-Dimethylpiperidine	**11a**	$CHCl_3$	8.6		331.3	
		$CHCl_3/CH_3OH$	7.7		332.5	
		CH_3OH	4.3		337.6	−6.6
4,4-Dimethylpiperidine	**12a**	$CHCl_3$	11.9		330.0	
		CH_3OH	6.4		334.3	−3.9
2,2,6,6-Tetramethylpiperidine	**13a**	$CHCl_3/CH_3OH$	7.6		295.6	
		CH_3OH	4.4		296.1	+3.5
2-Azaadamantane	**14a**	$CH_3OH/CHCl_3$[f]	4.9		319.7	+2.4
trans-Decahydroquinoline	**15a**	$CHCl_3/CH_3OH$	7.9		319.6	
		CH_3OH	4.5		322.5	
cis-Decahydroquinoline	**16a**	$CHCl_3/CH_3OH$	7.9		325.0	
		CH_3OH	4.5		328.5	
8-(e)-Methyl-*trans*-decahydroquinoline	**17a**	CH_3OH	5.5		326.0	
Pyrrolidine	**18a**	$CHCl_3$	10.7		322.2	
		CH_3OH	5.7		327.2	−9.1
N-Methylpiperidine	**1b**	$CHCl_3$	7.7		327.9	
		CH_3OH	4.0		329.1	−5.3
N,2-Dimethylpiperidine	**2b**	$CHCl_3$	8.6	Trans	319.4	
				Cis	324.7	
		CH_3OH	5.1	Trans	319.7	−3.4
				Cis	325.9	
N,3-Dimethylpiperidine	**3b**	$CHCl_3$	9.7	Cis	326.5	
				Trans	331.9	
		CH_3OH	4.0	Cis	327.8	−6.6
N,4-Dimethylpiperidine	**4b**	$CHCl_3$	9.7	Trans	327.8	
				Cis	330.2	
		CH_3OH	4.2	Trans	329.0	−5.6
N,(*cis*-2,6)-Trimethylpiperidine	**5b**	$CHCl_3$	8.7	NCH_3 eq	311.4	
				NCH_3 ax	318.1	
		CH_3OH	4.5	NCH_3 eq	310.4	−0.6
				NCH_3 ax	317.9	
N,(*trans*-2,6)-Trimethylpiperidine	**6b**	$CHCl_3$	9.0		316.5	
		CH_3OH	4.3		316.0	−9.5
N,(*cis*-3,5)-Trimethylpiperidine	**7b**	$CDCl_3$	8.9	NCH_3 eq	325.7	
				NCH_3 ax	330.4	
		CH_3OH	4.6	NCH_3 eq	327.1	−7.1
N,(*trans*-3,5)-Trimethylpiperidine	**8b**	$CHCl_3$	9.0		329.7	
		CH_3OH	4.6		332.8	−8.9
N,(*cis*-2,3)-Trimethylpiperidine	**9b**	$CHCl_3$	8.1	Cis/cis	321.1	
				Trans/cis	324.3[g]	
		CH_3OH	4.7	Cis/cis	321.9	
				Trans/cis	324.7[g]	

Table I (*Continued*)

Amine		Solvent[a]	Concn[b]	Isomer[c]	$\delta^{15}N$[d]	$\Delta\delta(H^+)$[e]
N,(*trans*-2 3)-Trimethylpiperidine	**10b**	$CHCl_3$	8.1	NCH_3 eq	318.7	
				NCH_3 ax	324.5[g]	
		CH_3OH	4.7	NCH_3 eq	319.4	
				NCH_3 ax	325.9[g]	
N,3,3-Trimethylpiperidine	**11b**	$CHCl_3$	7.7		329.0	
		CH_3OH	4.0		331.4	−7.3
N,4,4-Trimethylpiperidine	**12b**	$CHCl_3$	7.9		327.8	
		CH_3OH	4.4		328.7	
N,2,2,6,6-Pentamethylpiperidine	**13b**	$CHCl_3$	7.9		305.3	
		CH_3OH	4.1		302.9	−15.6
N-Methyl-2-azaadamantane	**14b**	$CHCl_3$	7.9		320.0	
		CH_3OH	4.9		320.0	−11.3
N-Methyl-*trans*-decahydroquinoline	**15b**	$CHCl_3$	10.7	NCH_3 eq	319.7	
				NCH_3 ax	325.8	
		CH_3OH	5.1	NCH_3 eq	320.4	−4.3
				NCH_3 ax	327.2	
N-Methyl-*cis*-decahydroquinoline	**16b**	$CHCl_3$	9.5	N inside	325.5	
				N outside	321.3	
		CH_3OH	5.0	N inside	327.8	−7.6
				N outside	322.2	
N-Methyl-8-(e)-methyl-*trans*-decahydroquinoline	**17b**	$CHCl_3$	5.7		327.8	
		CH_3OH	5.0		330.6	
N-Methylpyrrolidine	**18b**	$CHCl_3$	11.3		317.6	
		CH_3OH	4.9		319.5	−10.7
N-Ethylpiperidine	**19**	$CHCl_3$	8.2		320.0	
		CH_3OH	4.2		319.8	−2.2
N-Isopropylpiperidine	**20**	$CHCl_3$	9.0		314.4	
		CH_3OH	4.2		313.0	−5.0
3-Methylquinolizidine	**21**	$CHCl_3$	12.1	3-CH_3 eq	313.8	
				3-CH_3 ax	318.8	
		CH_3OH	5.1	3-CH_3 eq	313.7	
				3-CH_3 ax	320.0	
Quinuclidine	**22**	CH_3OH	4.0		342.3	−13.7

[a] Unless otherwise indicated, $CHCl_3/CH_3OH$ corresponds to 82 mol % $CHCl_3$, 18 mol % CH_3OH. [b] Mol % of solute. [c] Stereoisomer corresponding to specified configuration of *N*-methyl group where two isomers were observed, the major one is listed first. [d] The ^{15}N shift of the amine hydrochloride upfield from 1 M $H^{15}NO_3$ in D_2O. [e] Protonation shift of amine in methanol, produced by adding 1 equiv of HCl. [f] 80 mol % CH_3OH, 20 mol % $CHCl_3$. [g] Peak assignments are interchangeable.

Table II. $^{15}N/^{13}C$ Shift Correlation Parameters of Amine Hydrochlorides

Amine hydrochlorides	Solvent	Slope[a]	Intercept[b]	*r*	*N*[c]
Secondary piperidines	$CHCl_3$	1.114	357.773	0.976	9
	$CHCl_3/CH_3OH$[d]	1.227	362.192	0.993	14
	CH_3OH	1.362	369.801	0.993	17
Tertiary piperidines	$CHCl_3$	1.113	363.299	0.987	24
	CH_3OH	1.389	374.432	0.992	22

[a] Opposite signs were used for the ^{15}N shifts (upfield from HNO_3) and for the ^{13}C shifts (downfield from Me_4Si), so the slope is positive. [b] Intercept on the ^{15}N axis, $\delta^{13}C$ 0. [c] Number of compounds in the correlation. [d] 82 mol % $CHCl_3$, 18 mol % CH_3OH.

of pyrrolidine (**18a**), and *N*-methylpyrrolidine (**18b**) do correlate in the same way as those of the piperidines,[2] their hydrochlorides show very large deviations from the $^{15}N/^{13}C$ correlation line of the piperidine hydrochlorides (Table III). The reason for this may be connected with the observation that the ^{13}C shifts of the β carbons of pyrrolidine have unusual protonation shifts.[7]

The solvent, concentration, and counterion effects on the ^{15}N chemical shifts of piperidine salts are rather complex. Some general trends, such as the upfield shifts in methanol and small, but relevant, changes of the slopes of the $^{15}N/^{13}C$ correlation lines, are evident from Tables I and II. Structural effects on the solvent shifts are reflected in the solvent dependence of the additive shift parameters (Table IV). A more extensive treatment of solvent effects on ^{15}N chemical shifts of saturated amines and their salts will be provided later.[9]

The correlation of the ^{15}N chemical shifts of the free amines with corresponding carbon shifts was, in many cases, complicated by fast nitrogen inversion of N-methylated piperidines.[2] Protonation slows such inversion sufficiently so that separate signals for both epimers could be observed. The slope of the $^{15}N/^{13}C$ shift-correlation line of the main group of *N*-methylpiperidines (1.82) was slightly different from the slope of the secondary amines (1.90), or of the minor group of tertiary amines (1.97) which are expected to have a high preference for the equatorial *N*-methyl conformation.[2] If these differences in slope are connected with the axial-equatorial *N*-methyl equilibrium, they suggest an increased population of

Table III. Deviations from Least-Squares Line of $^{15}N/^{13}C$ Shift Correlations of Amines and Hydrochlorides[a]

Amine		$\delta^{13}C$[b]	Isomer[c]	Hydrochlorides			Amines[e]	
				$CHCl_3$	$CHCl_3/CH_3OH$[d]	CH_3OH	C_6H_{12}	CH_3OH
Piperidine	**1a**	27.4			2.7	2.3	0.7	0.6
2-Methylpiperidine	**2a**	36.1		0.5	0.9	1.5	0.03	−0.1
3-Methylpiperidine	**3a**	26.9		0.9	0.6	0.6	0.4	−0.2
4-Methylpiperidine	**4a**	26.7		1.9	1.8	1.8	0.6	0.4
cis-2,6-Dimethylpiperidine	**5a**	45.0			0.3	−0.1	−1.5	−1.2
trans-2,6-Dimethylpiperidine	**6a**	41.7			0.3	−0.02	1.8	0.9
cis-3,5-Dimethylpiperidine	**7a**	26.8		−0.2	−1.0	−1.2	−0.5	−1.3
trans-3,5-Dimethylpiperidine	**8a**	21.1		−0.8	−1.9	−2.4	−0.3	−0.4
cis-2,3-Dimethylpiperidine	**9a**	31.8		−1.4	−0.7	−0.9	2.7	
trans-2,3-Dimethylpiperidine	**10a**	36.4		−0.5	0.7	0.3	0.1	
3,3-Dimethylpiperidine	**11a**	22.9		−0.6	−1.6	−1.0	−0.6	−0.3
4,4-Dimethylpiperidine	**12a**	27.0		2.6		1.3	1.3	1.1
2,2,6,6-Tetramethylpiperidine	**13a**	53.1			−1.4	−1.5	5.6	2.6
2-Azaadamantane	**14a**	38.2				1.9[f]	0.7	0.4
trans-Decahydroquinoline	**15a**	34.7			−0.02	−0.05	−0.6	
cis-Decahydroquinoline	**16a**	29.8			−0.6	−0.7	−3.6	
8-(e)-Methyl-*trans*-decahydroquinoline	**17a**	31.0				−1.6	−2.2	
Pyrrolidine	**18a**	26.1		−6.2[g]		−7.1[g]	−0.03[g]	−2.1[g]
N-Methylpiperidine	**1b**	33.4		1.8		1.1	0.1	0.5
N,2-Dimethylpiperidine	**2b**	39.9	Trans	0.5		0.7	0.4	0.4
		34.8	Cis	0.1		−0.2		
N,3-Dimethylpiperidine	**3b**	33.1	Cis	0.04		−0.6	0.5	−0.02
		27.4	Trans	−0.9				
N,4-Dimethylpiperidine	**4b**	32.9	Trans	1.1		0.3	−0.4	−0.2
		30.5	Cis	0.8				
N,(*cis*-2,6)-Trimethylpiperidine	**5b**	46.5	NCH_3 eq	−0.2		0.6	−0.8	−0.3
		39.8	NCH_3 ax	−0.9		−1.2		
N,(*trans*-2,6)-Trimethylpiperidine	**6b**	41.9		−0.2		−0.2	8.5	6.3
N,(*cis*-3,5)-Trimethylpiperidine	**7b**	33.0	NCH_3 eq	−0.9		−1.5	−0.1	−0.4
		28.9	NCH_3 ax	−0.7				
N,(*trans*-3,5)-Trimethylpiperidine	**8b**	26.8		−3.8[g]		−4.4[g]	−0.2[h]	−0.2[h]
N,(*cis*-2,3)-Trimethylpiperidine	**9b**	37.5	Cis/cis	−0.5		−0.4		
		33.7	Trans/cis	−2.3[g]		−3.9[g]		
N,(*trans*-2,3)-Trimethylpiperidine	**10b**	39.5	NCH_3 eq	−0.6		−0.2	1.5	
		34.0	NCH_3 ax	−1.0		−1.3		
N,3,3-Trimethylpiperidine	**11b**	28.6		−2.5[g]		−3.3[g]	−0.3[h]	0.4[h]
N,4,4-Trimethylpiperidine	**12b**	32.8		1.0		−0.2	−0.9	
N,2,2,6,6-Pentamethylpiperidine	**13b**	50.0[i]		−2.4		−2.1	17.0	13.3
N-Methyl-2-azaadamantane	**14b**	39.4		0.5		0.3	10.4	7.8
N-Methyl-*trans*-decahydroquinoline	**15b**	38.4	NCH_3 eq	−0.9		−0.8	−0.03	−0.6
		34.0	NCH_3 ax	0.3		0.01		
N-Methyl-*cis*-decahydro-;quinoline	**16b**	30.0[i]	N inside	−4.4[g]		−5.0[g]	0.5[h]	−0.2[h]
		37.2	N outide	−0.6		−0.6		
N-Methyl-8-(e)-methyl-*trans*-decahydroquinoline	**17b**	26.6		−5.9[g]		−6.9[g]	1.3	
N-Methylpyrrolidine	**18b**	35.4		−6.3[g]		−5.8[g]	0.7	−0.3
N-Ethylpiperidine	**19**	40.6		1.9		1.8	−0.2	0.5
N-Isopropylpiperidine	**20**	44.9[k]		1.1		0.9	4.7	3.9
3-Methylquinolizidine	**21**	43.5	3-CH_3 eq	−1.1		−0.3	−0.2[h]	
		239.2[i]	3-CH_3 ax	−0.9		0.03	0.2[h]	
Quinuclidine	**22**	24.4				1.8	7.6	

[a] $\delta^{15}N$(experimental) − $\delta^{15}N$(calculated from slope/intercept). [b] Carbon shift (downfield from Me_4Si) of the analogous cyclohexane taken from ref 4. [c] Stereoisomer corresponding to specified configuration of *N*-methyl group; where two were observed, the major isomer is listed first. [d] 82 mol % $CHCl_3$, 18 mol % CH_3OH. [e] Values from ref 2. [f] 80 mol % CH_3OH, 20 mol % $CHCl_3$. [g] Shift excluded from least-squares error analysis. [h] Compounds which formed a separate $^{15}N/^{13}C$ correlation line as free bases. [i] Calculated carbon shift. [k] Shift of Cl of bicyclohexyl.

the axial *N*-methyl conformation for piperidines with 2,6 substituents.[10] Because for the amine hydrochlorides we can correlate the shifts of the particular stereoisomers with different configurations at nitrogen and not an equilibrium mixture as with the amines, it is expected and found that for the salts the correlation lines for tertiary and secondary derivatives are parallel in the same solvent.

A possible difficulty in making $^{15}N/^{13}C$ shift correlations, as has been done here, is whether or not the conformational equilibria between the possible chair conformations of the salts are equal, or at least similar, to those of the corresponding hydrocarbons. Thus, is the equilibrium constant for the interconversion of the *cis*-1,2-dimethylpiperidinium salt conformations unity, as it is for *cis*-1,2-dimethylcyclohexane?

No data appear to be available which indicate the positions of such equilibria for piperidine salts undergoing ring inversion. We have assumed, for the $^{15}N/^{13}C$ shift correlations and for the substituent-parameter calculations (see below), that these equilibria are close to 1:1 ratios expected for the analogous methylcyclohexanes of the hydrochlorides of *cis*-*N*,2-, *trans*-*N*,3-, and *cis*-*N*,4-dimethylpiperidines (**2b, 3b, 4b**). That the assumption is reasonable is indicated by the relatively small deviations of the ^{15}N shifts of these hydrochlorides from correlation lines (Table II).

Table IV. Substituent Parameters for Correlation of the ^{15}N NMR Shifts of Piperidines and Piperidine Hydrochlorides and ^{13}C NMR Shifts of Cyclohexanes

Parameter[a]	Piperidine hydrochlorides[b] $CHCl_3$	Piperidine hydrochlorides[b] CH_3OH	Piperidines[c]	Cyclohexanes[d]
Base shift	+329.7 (0.2/28)	+335.0 (0.2/28)	+337.0	−27.0
α^{eq}	−2.3 (0.2/19)	−5.9 (0.3/16)	−2.2	−6.0
α^{ax}	+3.9 (0.3/8)[e]	+0.3 (0.3/8)[e]	+20.2	−1.4
β^{eq}	−12.0 (0.2/11)	−13.2 (0.2/13)	−17.8	−9.0
β^{ax}	−8.4 (0.3/7)		−9.0	−5.4
γ^{eq}	−1.3 (0.1/28)		+0.5	−0.1
γ^{ax}	+4.5 (0.2/13)		+10.3	+6.4
$\alpha\beta$[f]	+4.3 (0.2/22)		+5.3 ($\alpha^{eq}\beta^{eq}$)	+2.5 ($\alpha^{eq}\beta^{eq}$)
			+13.5 ($\alpha^{eq}\beta^{ax}$)	+2.9 ($\alpha^{eq}\beta^{ax}$)
				+3.4 ($\alpha^{ax}\beta^{eq}$)
γ^{gem}	−1.2 (0.3/4)		−3.7	−2.0

[a] The same symbols are used as for the carbon parameters of cyclohexanes in ref 4b. [b] Standard deviation and number of occurrences in parentheses. Positive numbers represent upfield shifts. [c] Values from ref 2, not obtained by multilinear regression in cyclohexane as solvent. [d] Reference 4b. [e] The difference between α^{eq} and α^{ax} is the same for both solvents. The number of independent α parameters is therefore three: α^{eq} (CH_3OH), α^{eq} ($CHCl_3$), and $\Delta\alpha^{eq}\alpha^{ax}$. [f] This parameter is zero if both substituents are axial.

The axial/equatorial *N*-methyl equilibria of the 2,6-substituted piperidine hydrochlorides deserve special comment. ^1H and ^{13}C NMR spectra show that the equilibrium position changes in favor of the conformation with axial *N*-methyl if the number of equatorial substituents on α carbons is increased.[3,11] The equilibrium mixture of *N*,(*cis*-3,5)-trimethylpiperidine hydrochloride (**7b**) contains about 5% of the axial *N*-methyl epimer, while for *N*,(*cis*-2,6)-trimethylpiperidine hydrochloride (**5b**), which crystallizes as pure equatorial isomer, the equatorial/axial ratio is about 65:35 in solution. One possible explanation lies in the differences in nonbonded interactions for diequatorial and axial-equatorial-gauche interactions of vicinal substituents on six-membered rings. If so, then, in solutions of *N*,(*trans*-2,6)-trimethylpiperidine hydrochloride (**6b**), the conformer with an axial *N*-methyl group should have a population of much more than 35%. The interactions of the *N*-methyl group with the α-methyl groups change from diequatorial to two axial-equatorial interactions going from the trans to the cis isomer of **5b**. For **6b**, there is one diequatorial and one equatorial-axial interaction with equatorial *N*-methyl groups and one equatorial-axial for the isomer with axial *N*-methyl. The interac-

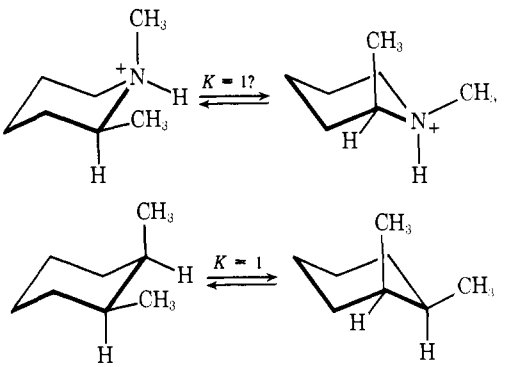


Table V. Substituent Parameters for Correlation of ^{15}N NMR Shift Changes Resulting from Protonation of Piperidines

Parameter	Value[a]	Deviation	N^b
Base shift	−3.1	0.3	21
α^{eq}	−2.1	0.4	11
β^{eq}	+4.1	0.4	7
β^{ax}	+0.5	0.8	2
γ^{eq}	−0.8	0.3	9
γ^{ax}	−4.1	0.5	5
$\alpha^{eq}\beta^{eq}$	−2.1	0.5	5
$\alpha^{eq}\beta^{ax}$	−6.8	1.1	1
γ^{gem}	+2.0	0.7	2

[a] Positive represents an upfield shift. [b] N = number of occurrences.

Table VI. ^{13}C NMR Chemical Shifts of Some Piperidine Hydrochlorides (ppm Downfield from Me_4Si and $CHCl_3$ Solutions)

Compd		Isomer	NCH_3	C(2)	C(6)	C(3)	C(5)	C(4)	CCH_3	
N-Methylpiperidine	**1b**		43.7	54.6	54.6	22.9	22.9	21.2		
N,2-Dimethylpiperidine	**2b**	Trans	40.9	61.2	55.9	31.5	23.2[a]	22.4[a]	17.8	
		Cis	36.6	56.6	50.7	27.3	20.4	18.9	13.7	
N,3-Dimethylpiperidine	**3b**	Cis	43.8	60.5	54.2	29.1	22.8	29.9	18.7	
		Trans	41.1	58.3	52.8	25.3	18.3[a]	31.1	18.2[a]	
N,4-Dimethylpiperidine	**4b**	Trans	43.7	54.6	54.6	31.1	31.1	28.4	21.0	
		Cis	41.3	50.4	50.4	27.6	27.6	25.3	18.3	
N,(*cis*-2,6)-Trimethylpiperidine	**5b**	N-CH_3 eq	36.6	62.3	62.3	32.0	32.0	22.7	18.4	
		N-CH_3 ax	24.4	59.6	59.6	25.1	25.1	22.6	17.7	
N,(*trans*-2,6)-Trimethylpiperidine	**6b**		37.8	56.6	55.3	29.9	28.4	17.24[a]	17.19[a]	12.1
N,(*cis*-3,5)-Trimethylpiperidine	**7b**	N-CH_3 eq	43.7	60.0	60.0	28.8	28.8	39.0	18.5	
		N-CH_3 ax	40.2?	57.1	57.1	24.4	24.4			
N,(*trans*-3,5)-Trimethylpiperidine	**8b**		44.6	60.6	58.7	27.2[a]	24.1[a]	35.7	18.7	18.1
N,3,3-Trimethylpiperidine	**11b**		44.7	64.2	54.5	31.1	19.9	34.5	29.4	24.5
N,2,2,6,6-Pentamethylpiperidine	**13b**		29.0	63.8	63.8	37.0	37.0	16.1	28.9	21.0
N-Methyl-2-azaadamantane	**14b**	N-CH_3 eq	39.6	55.5	55.5	33.8	33.8	25.0[a]	35.1(C-δ)	
		N-CH_3 ax				28.4	28.4	24.4[a]		

[a] Shift assignments interchangeable.

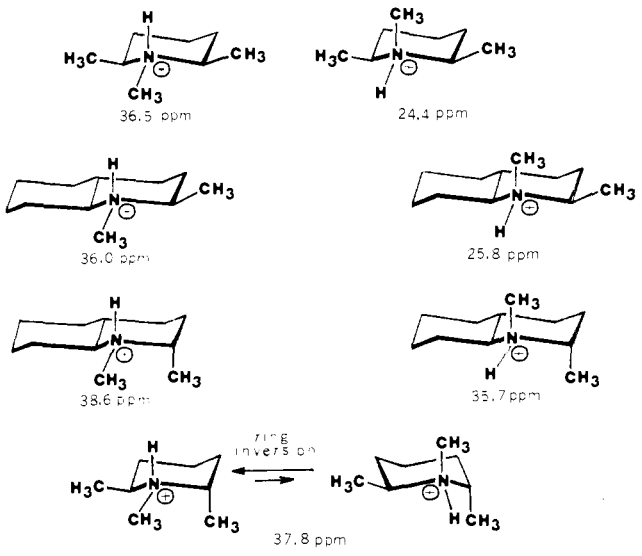
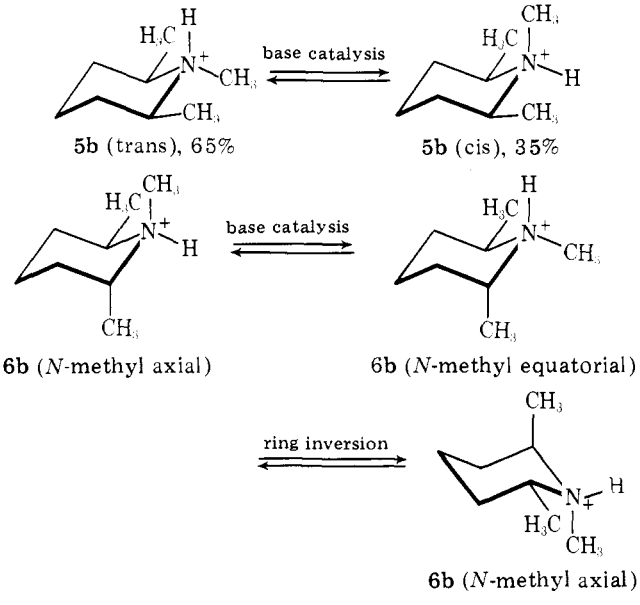


Figure 4. ^{13}C chemical shifts of N-methyl groups in cyclic amines.

tions of the axial *N*-methyl group with the ring carbons should be similar for both **5b** and **6b**. While for **5b** the base-catalyzed nitrogen inversion is sufficiently slow to allow the observation of separate NMR signals, the competing fast ring inversion of **6b** leads to averaged signals and thwarts simple determination of the position of equilibrium by measurement of signal intensities.



However, the nitrogen-15 chemical shift and the carbon-13 chemical shift of the *N*-methyl group of **6b** suggest a high proportion of the equatorial conformation. The argument follows: With regard to the ^{15}N chemical shift, in both chloroform and methanol, this shift correlates well with the experimental C2 carbon shift (41.9 ppm) of 1-*cis*-2-*trans*-3-trimethylcyclohexane, where the diequatorial-axial conformation is expected to be favored by about 9:1 over the diaxial-equatorial conformation. If the calculated ^{13}C shift of the diaxial-equatorial conformation of this 1,2,3-trimethylcyclohexane isomer (39.5 ppm) is used for the $^{15}N/^{13}C$ shift correlation of *N*,(*trans*-2,6)-trimethylpiperidine hydrochloride (**6b**), the deviation of the ^{15}N shift from the correlation line goes from −0.2 ppm (nitrogen scale) to 2.8 ($CHCl_3$) and 3.5 ppm (CH_3OH). The ^{13}C chemical shift of the *N*-methyl group of **6b** compared with the shifts of the two epimers of *N*-methyl-2-(a)-methyl-*trans*-decahydroquinoline hydrochloride[8b] (Figure 4) also indicates a strong preference for the conformation with equatorial *N*-methyl. Thus, the ^{13}C shift of 37.8 ppm for the piperidine salt, **6b**, is much closer to the ^{13}C shift of the equatorial *N*-methyl isomer of the conformationally fixed decalin (38.6 ppm) than to that of the axial epimer (35.7 ppm). If **6b** favors the equatorial position for the *N*-methyl, it seems possible only to conclude that the relatively high percentage of axial *N*-methyl group in solutions of *N*,(*cis*-2,6)-trimethylpiperidine hydrochloride (**5b**) must be the result of other than steric interactions. A very recent report[11d] suggests that the real cause is solvent interactions with the acidic NH proton.

The 56 ^{15}N chemical shifts of piperidine and *N*-methylpiperidine hydrochlorides in chloroform and methanol, excluding the values of 2,2,6,6-tetramethylpiperidine hydrochloride (**13a**), and its *N*-methyl derivative, **13b**, were used to calculate a set of additive substituent parameters by means of a multilinear regression analysis similar to the one done by Grant and co-workers[4b] for the ^{13}C chemical shifts of cyclohexanes. Nine independent substituent parameters, three of them duplicate to account for solvent effects, were needed to correlate all of the shifts. The values, mean deviations, and the number of occurrences of each parameter are listed in Table IV together with the values found for the free bases[2] and the ^{13}C shifts of cyclohexanes. The addition of other parameters, e.g., δ parameters, or the differentiation of the $\alpha\beta$ parameter into $\alpha^{eq}\beta^{eq}$, $\alpha^{eq}\beta^{ax}$, and $\alpha^{ax}\beta^{eq}$ parameters did not afford significant improvement of the correlation. The overall correlation coefficient of the linear regression analysis was 0.9976, and the standard deviation of the calculated shifts 0.5 ppm. The substituent parameters for the ^{15}N chemical shifts of piperidine hydrochlorides are in general smaller than the ones found for the free bases and are much closer to the values of the parameters describing the substituent effects on ^{13}C chemical shifts of cyclohexanes. Notably different from the carbon parameters are the downfield effects of equatorial γ-methyl groups and the small upfield γ^{ax} parameter.

If both the ^{15}N chemical shifts of the amines and their hydrochlorides can be described by sets of additive substituent parameters, the same should be possible for the protonation shifts listed in Table I. The correlation is, however, expected to be less good, because the errors of two different measurements are involved. In making the correlation, where protonation leads to two epimeric salts, the epimer corresponding to the major conformation of the amine was taken to determine the protonation shift. The nine parameters needed to describe 23 protonation shifts in methanol are listed in Table V. The correlation coefficient was 0.9886 and the standard deviation 0.7 ppm. The generally negative (downfield) protonation shift is increased by α and γ substituents but decreased or changed to upfield by β carbons. The orientation dependence of substituent effects on the protonation shifts is particularly important. Axial β carbons have a smaller effect than equatorial β carbons, but axial γ carbons have a bigger influence than equatorial γ carbons. The effect on the ^{15}N chemical shifts of free amines with carbon–carbon bonds antiperiplanar to the lone pair is the cause of the large $\alpha^{eq}\beta^{ax}$ shift parameter for protonation of such compounds.

A number of ^{13}C chemical shifts of *N*-methylpiperidine hydrochlorides were measured in this work and are listed in Table VI. The peak assignments were made by means of signal intensities, off-resonance decoupling, and by applying qualitatively the additivity rules found for methylcyclohexanes.[4b]

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trans-decahydroquinoline. We are also indebted to Dr. André Gagneux of Ciba-Geigy AG, Basel, who provided a sample of 2-azaadamantane, to Professor Robert T. LaLonde of the College of Environmental Science and Forestry, State University of New York at Syracuse, for the sample of 3-methylquinolizidine, and to Dr. D. K. Dalling of the University of Utah for calculations of ^{13}C chemical shifts of decalins.

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Steric and Electronic Effects on ^{15}N Chemical Shifts of Saturated Aliphatic Amines and Their Hydrochlorides[1]

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Abstract: Natural-abundance ^{15}N NMR chemical shifts of saturated aliphatic primary, secondary, and tertiary amines and their hydrochlorides have been measured in different solvents. Good linear correlations of these ^{15}N shifts with the ^{13}C shifts of carbons in the same positions in the corresponding hydrocarbon analogues were only found for the primary compounds. The degree of correlation between ^{15}N and ^{13}C shifts decreased successively with secondary to tertiary amines and their hydrochlorides. Despite this, sets of solvent-dependent additive shift parameters were derived which give reasonably satisfactory agreement between calculated and experimental shifts of all of the amines and hydrochlorides. Some of the substituent-induced shifts appear to be conformational effects and can be compared with substituent effects observed previously for cyclic amines. The generally downfield protonation shifts could also be correlated with empirical substituent parameters.

I. Introduction

In previous reports on the natural-abundance ^{15}N spectra of saturated amines, it was shown that the nitrogen chemical shifts of primary and secondary amines could be correlated with a set of additive substituent-effect parameters.[2] Also, it was found that for a variety of saturated acyclic compounds the ^{13}C chemical shifts of a particular carbon could be correlated with the ^{15}N shifts of primary and secondary amines of corresponding structures where nitrogen replaces the particular carbon.[2a]

More recently, the ^{15}N chemical shifts of methyl-substituted secondary and tertiary piperidines[3a] and their hydrochlorides[3b] were shown to be well described by substituent-shift parameters which have a close parallel to the parameters derived for calculation of ^{13}C chemical shifts of methylcyclohexanes.[4] Separate linear ^{15}N-shift correlations with the ^{13}C shifts of the hydrocarbon analogues were demonstrated for the secondary and the tertiary piperidines and some related compounds. The tertiary amines were different from the secondary amines in being split into a minor and a major group having different $^{15}N/^{13}C$ correlation lines. There were also some tertiary amines which showed large deviations from either correlation line. The discrepancies were related to a stereoelectronic shift effect associated with having the lone pair on nitrogen antiperiplanar with respect to one or more carbon–hydrogen bonds on the α carbons. Protonation was found to cancel this stereoelectronic effect and resulted in a change of the slopes of the $^{15}N/^{13}C$ shift-correlation lines from 1.9 (for the free amines in cyclohexane) to 1.1 (for the hydrochlorides in chloroform) and 1.4 (for the hydrochlorides in methanol). Furthermore, protonation diminished the upfield displacement of the correlation line of the tertiary amines from the correlation line for secondary amines from 12.5 ppm (free amines in cyclohexane) to 3.5 ppm (hydrochlorides in methanol). Most secondary and all tertiary piperidine hydrochlorides had downfield protonation shifts in methanol. The ^{15}N chemical shifts of tertiary amine hydrochlorides with gauche γ-carbon substituents as well as pyrrolidine and *N*-methylpyrrolidine hydrochlorides showed substantial deviations from the $^{15}N/^{13}C$ shift-correlation lines.

In the present research, the studies of shift correlations of natural-abundance ^{15}N NMR of saturated cyclic amines have been further extended to aliphatic primary, secondary, and tertiary amines. A priori, one might expect results similar to those for the cyclic amines, especially because quite useful ^{13}C substituent-effect parameters have been developed for aliphatic hydrocarbons.[5] The principal difficulty to be expected lies in the fact that the conformational equilibria of saturated amines are different from those of the analogous hydrocarbons. Thus, the preferred conformation of propylamine around the C1–C2 bond is gauche, while for butane, the anti conformation is fa-

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