Natural-Abundance Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy. Steric and Electronic Effects on Nitrogen-15 Chemical Shifts of Piperidines and Decahydroquinolines[1a]

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Abstract: Natural-abundance ^{15}N-NMR chemical shifts of closely related methyl-substituted piperidines, decahydroquinolines, and their *N*-methyl derivatives have been measured in cyclohexane and methanol. For both solvents, the secondary amines and two groups of tertiary amines give separate linear correlations with the ^{13}C chemical shifts of their hydrocarbon analogues. Additive shift parameters for carbon substituents near nitrogen, similar to those which correlate ^{13}C chemical shifts, have been determined. Except for the *N*-alkylation parameters, these parameters are relatively solvent insensitive, at least for cyclohexane and methanol. Nonetheless, ^{15}N chemical-shift comparisons are best made for the same solvent or very similar solvents. A large shift effect results when substituents are changed which are antiperiplanar to the orbital of the unshared electrons of tertiary amines. The use of the additive shift parameters and the general correlation between ^{15}N and ^{13}C shifts with respect to analysis of conformational and structural changes is illustrated using *N*-methylpiperidine and *cis*-2,3-dimethylpiperidine as specific examples.

Introduction

In a previous report 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 the ^{13}C shifts of a variety of saturated acyclic compounds could be correlated with the ^{15}N shifts of primary and secondary amines of corresponding structures. What this means is that the C1 shift of butane correlates with the ^{15}N shift of propylamine, the C2 shift of butane with the ^{15}N shift of methylethylamine, etc. The purpose of the present work was to extend the same analysis to the ^{15}N shifts of a series of methylpiperidines and decahydroquinolines, as well as their *N*-methyl derivatives.

A useful set of empirical additive structural parameters has been obtained for the carbon shifts of methylcyclohexanes,[3] and if there is a reasonable linear correlation between carbon shifts of cyclohexanes and the nitrogen shifts of analogously substituted methylpiperidines, it should be possible to derive a similar parameter set for the ^{15}N shifts of substituted piperidines as well. However, there is a number of possible reasons why nitrogen and carbon shifts may not correlate:

(1) Steric effects on the shifts arising from proton–proton interactions might be quite different from those arising from proton–lone pair interactions. (2) Differential solvent effects, especially when hydrogen bonding is important, may be expected even for very simple saturated amines.[4] (3) The degree of σ delocalization of the lone pair by hyperconjugation or the extent of inductive polarization of the σ electrons could change with the pattern of hydrogen–carbon substitution and conformation with respect to the lone pair and the size of the lone-pair orbital.[5] (4) Differences in energy of $n \rightarrow \sigma^*$ transitions could produce sizable shift effects arising from changes in the second-order paramagnetic effect with changes in structure.

Experimental Section

Nitrogen-15 chemical shifts were measured with a Bruker WH-180 FT-NMR spectrometer operating at 18.25 MHz. Except as indicated, the spectra were taken of 20 mol % (~2 M) solutions in cyclohexane and 8 mol % (~2 M) in methanol at the ambient probe temperature (35–40 °C with proton noise decoupling). The 25-mm tubes were fitted with a Teflon vortex plug which held a concentric 5-mm tube containing 1 M ^{15}N-enriched nitric acid in D_2O which served both as a reference and as the deuterium lock signal. The solutions were not degassed. Chemical shifts are reported in parts per million *upfield* from $H^{15}NO_3$ and in general are reproducible to the precision of the data system (1.25 Hz ~ 0.1 ppm). To obtain a signal-to-noise ratio of greater than 3:1, 500 to 1000 15° pulses were accumulated. This required for each spectrum, depending on the relaxation time of the amine being examined, from 30 min (for a 2-s repetition rate) to 5 h (for a 17-s repetition rate). The half-width of the resonance signals ranged from 1 to 10 Hz. Secondary amines generally gave broader signals than tertiary amines. Peak assignments for isomer mixtures were made by comparison with the shift of one pure isomer or by comparing mixtures with known and different compositions. Peak intensities were in good agreement with the ratios determined by other methods.

Except as noted below, the samples were commercially available compounds (Aldrich Chemical Co., and Eastman Kodak Co.). Liquid amines were freshly distilled from calcium hydride and solids were sublimed before measurement. Secondary amines were converted to *N*-methyl tertiary amines by the Leuckart method.[6]

Carbon-13 NMR spectra were taken of 10% solutions in deuteriochloroform, using a Varian XL-100, and proton spectra were taken with a Varian A-60 spectrometer.

3,3- (11a) and 4,4-Dimethylpiperidine (12a) were prepared according to the procedure of Hoch and Karrer.[7]

Mixtures of the stereoisomeric **2,6- (5a, 6a), 3,5- (7a, 8a)**, and **2,3-dimethylpiperidines (9a, 10a)** were obtained by sodium and ethanol reduction of dimethylpyridines by a procedure described for the reduction of pyridine.[8]

Catalytic hydrogenation of *N*-3,5-trimethylpyridinium iodide yielded a mixture of ***N*-methyl-*cis*-** and ***N*-methyl-*trans*-3,5-dimethylpiperidines (7b, 8b)**.[9a] ***N*-Isopropylpiperidine (20)** was prepared in the same way.[9b] It was found advantageous to shake the solutions before hydrogenation for 24 h with Raney-nickel C.[10]

8(e)-Methyl-*trans*-decahydroquinoline (17a), also recently reported by Eliel and co-workers,[11] was synthesized by methylation of $\Delta^{1,9}$-octahydroquinoline[12] following a method of Evans and Domeier,[13] and subsequent reduction of the imine double bond with sodium in ethanol. The product was shown by proton, carbon, and nitrogen NMR to be contaminated with *trans*-decahydroquinoline (**15a**) and minor amounts of two other methyl-*trans*-decahydroquinolines which were not characterized further.

Results and Discussion

The ^{15}N chemical shifts of various methylpiperidines, decahydroquinolines, related compounds, and their *N*-methyl

Table I

Compound	No.	Solvent	$\delta(^{15}N)^l$ a NH	$\delta(^{15}N)^l$ b NCH_3	$\delta(^{13}C)^m$ CH_2	$\delta(^{13}C)^m$ $CHCH_3$
Piperidine	**1**	C_6H_{12}	336.3	336.6	−27.4[a]	−33.4[a]
		CH_3OH	337.0	334.4		
2-Methylpiperidine	**2**	C_6H_{12}	319.1	325.1	−36.1[a]	−39.9[a]
		CH_3OH	320.6	323.1		
3-Methylpiperidine	**3**	C_6H_{12}	337.0	337.6	−26.9[a]	−33.1[a]
		CH_3OH	337.1	334.4		
4-Methylpiperidine	**4**	C_6H_{12}	337.5	337.0	−26.7[a]	−32.9[a]
		CH_3OH	338.0	334.6		
cis-2,6-Dimethylpiperidine	**5**	C_6H_{12}	300.7	311.9	−45.0[a]	−46.5[a]
		CH_3OH	303.5	311.0		
trans-2,6-Dimethylpiperidine	**6**	C_6H_{12}	310.2	329.6	−41.7[a]	−41.9(eq)[b]
		CH_3OH	311.5	325.5		−39.5(ax)[b]
cis-3,5-Dimethylpiperidine	**7**	C_6H_{12}	336.5	337.2	−26.7[a]	−33.0[a]
		CH_3OH	336.4	334.2		
trans-3,5-Dimethylpiperidine	**8**	C_6H_{12}	347.3	345.1	−21.1[a]	−26.8[a]
		CH_3OH	347.4	341.7		
cis-2,3-Dimethylpiperidine	**9**	C_6H_{12}	329.9		−31.8[a]	
trans-2,3-Dimethylpiperidine	**10**	C_6H_{12}	318.6	326.9	−36.4[a]	−39.5[a]
3,3-Dimethylpiperidine	**11**	C_6H_{12}	343.6	341.4	−22.9[a]	−28.6[a]
		CH_3OH	344.2	338.7		
4,4-Dimethylpiperidine	**12**	C_6H_{12}	337.7	336.7	−27.0[a]	−32.8[b]
		CH_3OH	338.2			
2,2,6,6-Tetramethylpiperidine	**13**	C_6H_{12}	292.3	323.3	−53.1[c]	−50.0(eq)[b]
		CH_3OH	292.6	318.5		−49.3(ax)[b]
2-Azaadamantane	**14**	C_6H_{12}		336.0	−38.2[d]	−39.4[d]
		C_6H_6	315.8			
		CH_3OH	317.3	331.3		
trans-Decahydroquinoline	**15**	C_6H_{12}	321.1	327.4	−34.7[e]	−38.4[e]
		CH_3OH		324.7		
cis-Decahydroquinoline	**16**	C_6H_{12}	331.6	339.5	−27.6[i]	−30.0[h]
		CH_3OH		335.4		
8(e)-Methyl-*trans*-decahydroquinoline	**17**	C_6H_{12}	326.6	350.2	−31.0[e]	−26.6[e]
Pyrrolidine	**18**	C_6H_{12}	337.3	333.6	−26.5[f]	−35.4[f]
		CH_3OH	335.9	330.2		

Compound	No.	Solvent	$\delta(^{15}N)^l$	$\delta(^{13}C)^m$
N-Ethylpiperidine	**19**	C_6H_{12}	323.2	−40.6[f]
		CH_3OH	322.0	
N-Isopropylpiperidine	**20**	C_6H_{12}	320.3	−44.9[k]
		CH_3OH	318.0	
3(e)-Methylquinolizidine	**21**	C_6H_{12}	312.2	−43.5[e]
3(a)-Methylquionolizidine	**22**	C_6H_{12}	321.1	−39.2[h]
cis-4-*tert*-Butylcyclohexylamine	**23**	C_6H_{12}	343.4	
		CH_3OH	343.5	
trans-4-*tert*-Butylcyclohexylamine	**24**	C_6H_{12}	334.6	
		CH_3OH	334.8	
2-Aminoadamantane	**25**	CH_3OH	340.3	
Atropine	**26**	$CHCl_3$	314.9	
Scopolamine	**27**	$CHCl_3$	336.4	
Quinuclidine	**28**	H_2O	356.0	
		C_6H_6	366.5	−24.4[g]

[a–g] ^{13}C shifts from ref 14a–g. [h] Calculated shifts. [i] Calculated shift using ΔG(for *N*-inside ⇄ *N*-outside conformations) = 1.06 kcal/mol obtained from the data in ref 15, the carbon shifts of slowly inverting *cis*-decalin (ref 14e), and assuming a temperature of 37 °C. [k] Shift of bicyclohexyl (ref 14f). [l] Upfield with respect to NHO_3. [m] Downfield with respect to TMS.

derivatives, measured in cyclohexane and methanol solutions, are given in Table I along with the ^{13}C chemical shifts of their hydrocarbon analogues.[14] A plot of the ^{15}N shifts vs. the corresponding ^{13}C shifts is shown in Figure 1 (for cyclohexane solutions) and in Figure 2 (for methanol solutions). (In order to have a positive slope, the carbon shifts which are downfield in respect to TMS were given a negative sign and the nitrogen shifts which are upfield from nitric acid a positive sign.)

It is obvious, that there is no linear relationship which includes all of the structures. This is in accord with our previous work,[2] where separate linear correlations were found between ^{15}N and ^{13}C chemical shifts for saturated acyclic primary and secondary amines. We now find that secondary heterocyclic amines are well correlated with a single line but that the tertiary amines divide into a major group and a minor group which are correlated by two different lines. The slopes, intercepts, and correlation factors corresponding to the data of Figures 1 and 2 are listed in Table II. The deviations of each nitrogen shift from the least-squares line are given in Table III. The nitrogen shifts of a few amines which do not appear to fall in any of the three correlating groups, or which have conformational equilibria of unknown position, have been excluded from the least-squares analysis. These compounds are marked in Table III. Their deviations have been determined from the slope and intercepts of the linear $^{15}N/^{13}C$ chemical-shift relations.

Table II

Compounds	Solvent	Slope[a]	Intercept[b]	Corr coef	No. of examples
Secondary piperidines	C_6H_{12}	1.902	387.73	0.9971	14
	CH_3OH	1.804	385.81	0.9986	11
Tertiary piperidines					
Group I	C_6H_{12}	1.819	397.30	0.9967	10
	CH_3OH	1.726	391.54	0.9988	8
Group II	C_6H_{12}	1.967	398.00	0.9997	5
	CH_3OH	1.955	394.24	0.9951	3

[a] δ (^{13}C) (downfield from tetramethylsilane, negative values) = X; $\delta(^{15}N)$ (upfield from HNO_3, positive values) = Y. [b] Intercept on ^{15}N chemical shift axis ($\delta(^{13}C) = 0$).

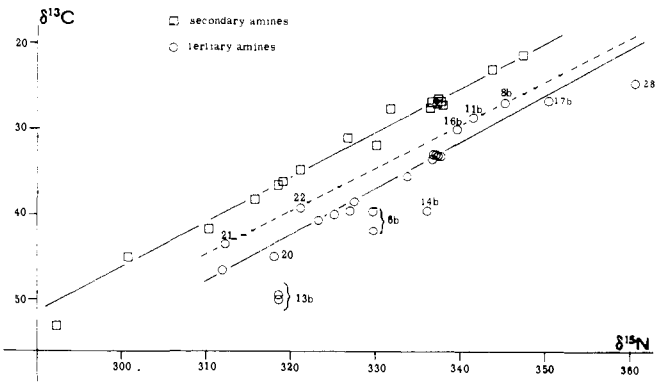


Figure 1. $^{15}N/^{13}C$ shift correlation (cyclohexane).

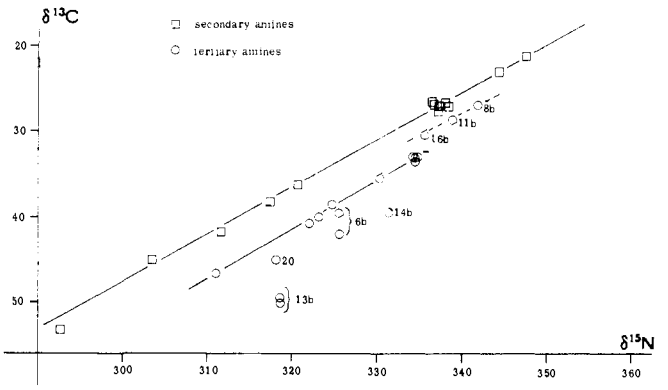
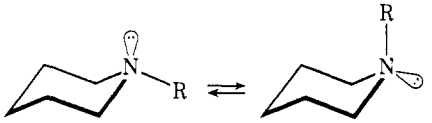


Figure 2. $^{15}N/^{13}C$ shift correlation (methanol).

The ^{15}N shifts which correlate well with the ^{13}C shifts can, of course, be expressed by substituent parameters to the same degree as the ^{13}C shifts. The rather small differences in the slopes of the correlation lines (Table II) indicate that the substituent parameters for each of the three groups and in both solvents have similar magnitudes. The intercepts show a pronounced solvent dependence, especially for the tertiary amines. Because the same carbon shifts were used for both solvents, the changes in intercept and slope reflect the solvent effects on ^{15}N chemical shifts of saturated amines. The solvent dependence makes it difficult to compare the slope and intercept with those previously found for acyclic secondary amines (1.67 and 380.5).[2] The effect which appears to be most solvent dependent is the α-alkylation parameter of secondary amines, and in the following discussion of shift parameters we will restrict ourselves to shifts measured in cyclohexane. An analogous treatment of the shifts for methanol solution can be easily carried through with the aid of the methanol shifts in Table I.

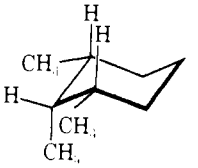
Analysis of structural influences on ^{15}N chemical shifts of *N*-alkylated piperidines must take account of possible conformational differences between piperidine (**1a**) and *N*-methylpiperidine (**1b**). Whether the lone pair of piperidine is



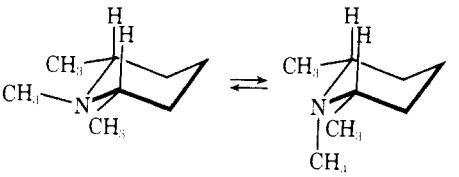
1a, R = H
1b, R = CH_3

most favorably axial or equatorial has been the subject of considerable controversy. Currently, there are reasonable arguments for a slight preference of the lone pair axial (60–70% at 25 °C) in the gas phase or in nonpolar solvents.[16a] To account for NMR evidence which indicates a possibility of strong preference for an equatorial lone pair, a change in conformational equilibria in going to polar solvents has been suggested,[16a] but has not as yet been confirmed. For *N*-methylpiperidine, predominance of the conformer with axial lone pair has never been questioned. Nonetheless, the reported equilibrium constants, obtained from different kinds of measurements, cover an even larger range than for piperidine. Thus, the degree of preference for axial methyl at room temperature has been determined to be: 25% by dipole moment measurements,[16c] 5–9% from ^{13}C chemical shifts,[16d] and about 1% from "fast protonation" in the gas phase or in cyclohexane solution.[16e]

We expect sizable ^{15}N chemical-shift differences between the two lone-pair conformations of piperidine (**1a**) and *N*-methylpiperidine (**1b**). One way in which ^{15}N and ^{13}C shifts could become uncorrelated is through the possibility of having the nitrogen assume a favorable conformation through inversion which would not be possible for an analogously situated carbon. Thus, while the methyl group on C2 of *cis,cis*-1,2,3-trimethylcyclohexane will surely be axial, the *N*-methyl of *cis*-2,6-dimethylpiperidine, **6**, can either be axial or equatorial.



cis,cis-1,2,3-trimethylcyclohexane



cis-2,6-dimethylpiperidine (**6**)

Obviously, a preferred choice for making the correlation would be the ^{13}C shift of the isomer in the carbon series which cor-

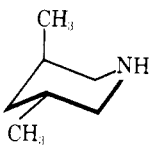
Table III

Compound	No.	Solvent	Deviation of ^{15}N shifts, ppm: a = secondary amines	b = tertiary amines: Group 1	b = tertiary amines: Group 2
Piperidine	**1**	C_6H_{12}	0.7	0.1	
		CH_3OH	0.6	0.5	
2-Methylpiperidine	**2**	C_6H_{12}	0.03	0.4	
		CH_3OH	−0.1	0.4	
3-Methylpiperidine	**3**	C_6H_{12}	0.4	0.5	
		CH_3OH	−0.2	−0.02	
4-Methylpiperidine	**4**	C_6H_{12}	0.6	−0.4	
		CH_3OH	0.4	−0.2	
cis-2,6-Dimethylpiperidine	**5**	C_6H_{12}	−1.5	−0.8	
		CH_3OH	−1.2	−0.3	
trans-2,6-Dimethylpiperidine	**6**	C_6H_{12}	1.8	8.5 (NCH_3 eq)[a]	
				4.2(NCH_3 ax)[a]	
		CH_3OH	0.9	6.3(NCH_3 eq)[a]	
				2.1(NCH_3 ax)[a]	
cis-3,5-Dimethylpiperidine	**7**	C_6H_{12}	−0.5	−0.1	
		CH_3OH	−1.3	−0.4	
trans-3,5-Dimethylpiperidine	**8**	C_6H_{12}	−0.3		−0.2
		CH_3OH	−0.4		−0.2
cis-2,3-Dimethylpiperidine	**9**	C_6H_{12}	2.7[a]		
trans-2,3-Dimethylpiperidine	**10**	C_6H_{12}	0.1	1.5	
3,3-Dimethylpiperidine	**11**	C_6H_{12}	−0.6		−0.3
		CH_3OH	−0.3		0.4
4,4-Dimethylpiperidine	**12**	C_6H_{12}	1.3	−0.9	
		CH_3OH	1.1		
2,2,6,6-Tetramethylpiperidine	**13**	C_6H_{12}	5.6[a]	17.0(NCH_3 eq)[a]	
				15.7(NCH_3 ax)[a]	
		CH_3OH	2.6[a]	13.3(NCH_3 eq)[a]	
				12.0(NCH_3 ax)[a]	
2-Azaadamantane	**14**	C_6H_{12}		10.4[a]	15.5
		C_6H_6	0.7		
		CH_3OH	0.4	7.8[a]	14.1
trans-Decahydroquinoline	**15**	C_6H_{12}	−0.6	−0.03	
		CH_3OH		−0.6	
cis-Decahydroquinoline	**16**	C_6H_{12}	−3.6[a]		0.5
		CH_3OH			−0.2
8(e)-Methyl-*trans*-decahydroquinoline	**17**	C_6H_{12}	−2.2	1.3[a]	4.5[a]
Pyrrolidine	**18**	C_6H_{12}	−0.03[a]	0.7[a]	
		CH_3OH	−2.1[a]	−0.3[a]	
N-Ethylpiperidine	**19**	C_6H_{12}		−0.2	
		CH_3OH		0.5	
N-Isopropylpiperidine	**20**	C_6H_{12}		4.7[a]	
		CH_3OH		3.9[a]	
3(e)-Methylquinolizidine	**21**	C_6H_{12}			−0.2
3(a)-Methylquinolizidine	**22**	C_6H_{12}			0.2
Quinuclidine	**28**	C_6H_6		+7.6[a]	+10.5[a]

[a] Shift not included in the least-squares analysis, deviation given is that calculated from the least-squares predicted shift based on the ^{13}C shift.

responds to the most favorable $N-CH_3$ conformation or, better, the weighted average of the ^{13}C chemical shifts of the appropriate stereoisomers which corresponds to the conformational equilibrium of the *N*-methyl group.

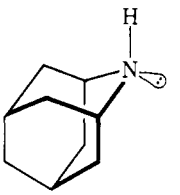
If there were large effects of this kind with the *secondary* piperidines, these should be evident in the correlation with the shifts of analogous carbons in the corresponding cyclohexanes. However, Figures 1 and 2 show that the deviations from the linear correlation are not large. This may mean that all the secondary piperidines have the same or similar axial-equatorial equilibrium positions for their nitrogen lone pairs or that the lone-pair conformational shift changes are linear with the other structural shift effects, or else, that the orientation of the lone pair for secondary piperidines has no important effect on the ^{15}N chemical shifts. The same or similar axial-equatorial lone-pair equilibrium positions for the different secondary piperidines studied here is unlikely, particularly because piperidines both with axial β- and γ-methyl groups were included. There is evidence that such substituents do, in fact, influence the lone-pair conformations.[17] The possibility of regular changes in conformation with structure is not supported by the shifts for substances such as 2-azaadamantane (**14a**) and 8(e)-methyl-*trans*-decahydroquinoline (**17a**). Of these, **14a** has a single conformation, while **17a** is expected,



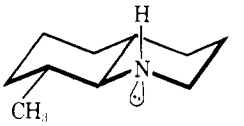
8a

1a

5a



14a



17a

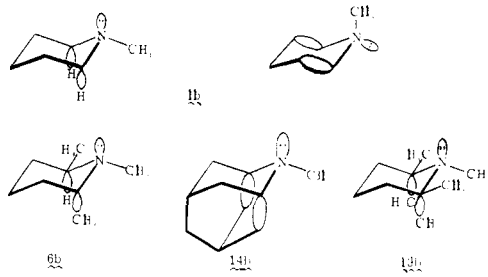


Figure 3. Configurations of piperidines showing antiperiplanar orientations of nitrogen lone pair and C–H or C–C σ-bond orbitals.

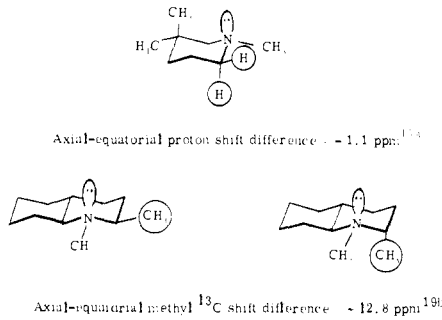
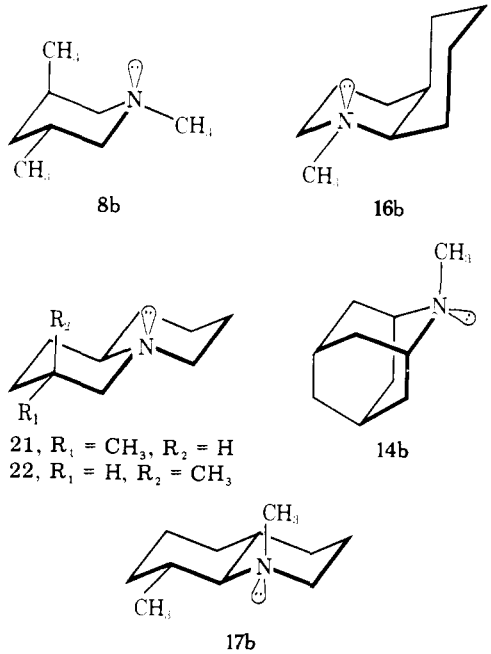


Figure 4. Proton and ^{13}C shift changes for antiperiplanar hydrogen and methyl groups.

through steric interactions, to have its N–H proton at least predominantly axial, and yet, the nitrogen-15 shifts of both substances correlate well with those of the other compounds. We can only conclude, at this point, that ^{15}N NMR shifts do not seem very helpful for determining the position of equilibrium for different lone-pair conformations of saturated *secondary* amines.

Analysis of the $^{15}N/^{13}C$ chemical-shift correlations for tertiary amines indicates a rather more complex situation (Figures 1 and 2).

Here, seven of the compounds are expected to strongly favor one conformation: the *N*-methylpiperidines having an axial γ-methyl group (**8b, 11b**); *N*-methyl-*cis*-decahydroquinoline (**16b**), and the two 3-methylquinolizidines **21** and **22**[18] should



8b **16b**

21, $R_1 = CH_3$, $R_2 = H$
22, $R_1 = H$, $R_2 = CH_3$

14b

17b

have equatorial *N*-alkyl substituents. The *N*-methyl is expected to be axial for 8(e)-methyl-*N*-methyl-*trans*-decahydroquinoline (**17b**), and whether or not the methyl group in *N*-methyl-2-azaadamantane (**14b**) is taken to be axial or equatorial, it will experience the steric and electronic interactions expected of an axial *N*-methyl.

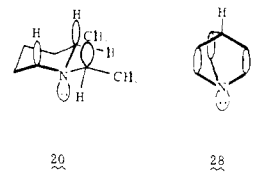


Figure 5. Orientations of nitrogen lone pair and σ-bond orbitals for *N*-isopropylpiperidine (**20**) and quinuclidine (**28**).

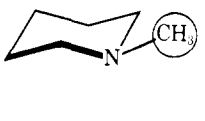
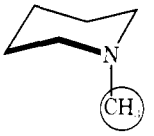
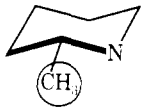
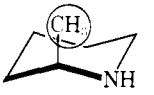
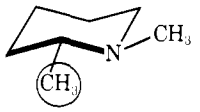
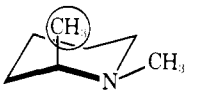
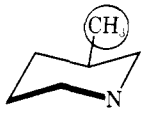
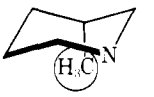
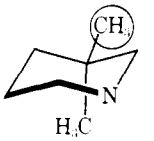
Although a good $^{13}C/^{15}N$ shift correlation is found for the tertiary piperidines with *N*-equatorial groups (group II, Table II), large deviations, +15.5 ppm (**14b**) and 4.5 ppm (**17b**), were found for the two cases with axial nitrogen methyl groups, with a few exceptions, the remaining *N*-methylpiperidines, for which the conformational preferences are not so extreme, give a good $^{15}N/^{13}C$ shift correlation with a quite different intercept and slope (group I, Table II). From all of this, it appears that the conformation at the nitrogen of *N*-methylpiperidines does have an important effect on ^{15}N chemical shifts, which results in changing the intercept and slope of the correlation with the ^{13}C chemical shifts of corresponding hydrocarbons.

The tertiary amines, which have large deviations from the group I and group II correlation lines, and the axial conformer of *N*-methylpiperidine share a common structural feature. This is having the lone-pair nitrogen orbital *antiperiplanar to the σ-bonding orbitals of C–C bonds* rather than *antiperiplanar to C–H bonds* as is the case with the other tertiary amines (see Figure 3). For these amines, special shift effects specific for nitrogen could be the result of n–σ^* interactions which would not be the same for C–C and C–H bonds. Corresponding and substantial shift effects on the resonances of protons and carbons antiperiplanar to lone pairs of cyclic tertiary amines have been accounted for by this kind of mechanism (Figure 4).[17a,19] Protonation of these amines reduces the shift differences between axial and equatorial protons and carbons to close to the values found for hydrocarbons.[17a,19b] Furthermore, one line now suffices for a linear $^{15}N/^{13}C$ shift correlation of the shifts of tertiary cyclic amine hydrochlorides, including axial *N*-methyl groups.[20] It also appears that the ^{15}N chemical shifts of the free bases measured in methanol, a solvent which hydrogen bonds strongly to the nitrogen lone pairs, have smaller deviations of the shifts from the correlation lines. Larger contact shifts with paramagnetic metal ions have been observed for nuclei antiperiplanar to the lone pair than for nuclei with other orientations.[21] *N*-Isopropylpiperidine (**20**) and quinuclidine (**28**) are further examples where possible conjugative interaction of the lone pair with C–C bonds, as in Figure 5, can account for the observed deviations from the ^{15}N–^{13}C shift-correlation line of 4.7 and 7.6 ppm, respectively.

Why are the antiperiplanar ^{15}N shift effects larger for tertiary than for secondary piperidines? Similar effects have been reported for carbon shifts.[19b] Thus, the change from equatorial to axial of the 2-methyl group in 2-methyl-*trans*-decahydroquinoline gives a 4.3 ppm upfield ^{13}C shift of the 2-methyl group (which, when axial, is antiperiplanar to the lone pair), but the corresponding stereochemical change with the *N*-methyl produces a 12.8 ppm ^{13}C shift of the 2-methyl (Figure 4). A possible reason is the difference in size and hybridization of the orbitals for the unshared electrons in secondary and tertiary amines.[5] This could also account for the different $^{15}N/^{13}C$ shift-correlation lines found for secondary and tertiary cyclic amines having equatorial *N*-methyl groups.

α-Substituent Parameters. Neglecting possible small shift

Table IV. Comparison of ^{15}N and ^{13}C Substituent Shift Parameters

Parameter	^{15}N[a]	^{13}C[b]	Parameter	^{15}N[a]	^{13}C[b]
	−2.2 ± 0.0 (2)	−6.0		+20.2 (1)	−1.4
	−17.8 ± 0.6 (2)	−9.0		−9.0 (1)	−5.4
	−12.5 ± 1.0 (2)	−6.5		+4.5 (1)	−2.5
	0.5 ± 1.0 (6)	−0.05		+10.3 (1)	+6.4
				−3.7 ± 0.0 (2)	−2.0

[a] Average values with deviations for nonpolar solvents. Parenthetical numbers refer to the number of examples run to obtain the average. [b] Reference 14b.

effects arising from the lone-pair orientations in the secondary piperidines, approximate *N*-methylation parameters can be derived from the shifts of Table I for nonpolar solvents. Thus, $\alpha^{eq} = -2.2$ *ppm* from compounds **8** and **11**, and $\alpha^{ax} = +20.2$ *ppm* from compound **14**. Only small shift changes, either up- or downfield, are observed on *N*-methylation of piperidine (**1a**) and those methylpiperidines that do not have β- or axial γ-methyl groups (**3a**, **4a**, **7a**, and **12a**). From this fact, and from shifts expected for equatorial and axial *N*-methylation derived above, the percentage of axial methyl group in *N*-methylpiperidine is estimated to be 10% (ΔG = 1.4 kcal/mol, T = 310 K). A similar value (ΔG = 1.35 − 1.77 kcal/mol) has been reported from the ^{13}C chemical shifts of piperidines and *trans*-decahydroquinolines.[16d]

N-Methylation of piperidines with equatorial methyl groups on the α carbons (**2**, **5**, **10**, and **15**) results in increased shielding. Part of this may be due to an increase of the conformer with an axial *N*-methyl group as suggested for α-alkylated piperidines,[16e] the rest to the gauche interactions between α and β carbons as will be discussed below in conjunction with the β-substituent effects. Very large upfield shifts are connected with the *N*-methylation of piperidines having axial β-methyl groups (**6**, **13**, and **14**). Possible causes have been discussed above. The largest effect, +31 ppm, was observed on *N*-methylation of 2,2,6,6-tetramethylpiperidine (**13b**).

The different steric environments of N substituents in five-membered rings make the *N*-methylation effect on the resonance of pyrrolidine (−3.6 ppm) different from that for piperidine (+0.3 ppm) and for this reason pyrrolidine (**18a**) and *N*-methylpyrrolidine (**18b**) were excluded from the $^{15}N/^{13}C$ shift correlation.

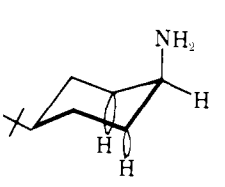
β-Substituent Parameters. The average shift effect produced by an equatorial β-methyl group, as observed for the secondary piperidines **2a** and **5a** (Table I) is -17.8 *ppm*. The β effect in simple primary amines is similar, −18.2 ppm.[2]

The β^{eq}-methyl effect on the ^{15}N chemical shifts of *N*-methylpiperidines appears to be reduced by the gauche diequatorial interaction of the N α and β substituents. Thus, a β^{eq}-methyl parameter of about 12 ppm is found for **1b** → **2b** and **2b** → **5b**.

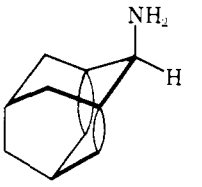
Gauche interactions between equatorial β- and γ-methyl groups cause only minor shift changes: −0.5 ppm for **2a** → **10a**; and +1.8 ppm for **2b** → **10b**. On this basis, comparison of the shifts of *trans*-decahydroquinoline (**15a**) with 3-methylpiperidine (**3a**) suggests an equatorial β-substitution effect of about −15.9 ppm.

The ^{15}N chemical-shift change from 2-methylpiperidine, **2a**, to *trans*-2,6-dimethylpiperidine, **6a**, yields an axial β-methyl parameter of about −9 ppm. The change from **2b** → **6b** is upfield by 4.5 ppm, a difference of 13.5 ppm, resulting from the effect of the axial β-methyl on the nitrogen shift of a tertiary amine as discussed above.

γ-Substituent Parameters. The spectra of piperidine (**1a**), 3-methyl-, and *cis*-3,5-dimethylpiperidine (**3a** and **7a**, respectively) show that equatorial γ-methyl groups have a negligibly small effect on ^{15}N chemical shifts. This is not quite as expected when account is taken of the influence of first-row heteroatoms on the chemical shifts of carbons antiperiplanar to the heteroatom.[22] Thus, the ^{13}C resonances of the γ-methyl groups of **3a** and **7a** are shifted upfield by about 4 ppm, as the result of what is thought to be a hyperconjugative effect of the nitrogen lone pair.[22] It is surprising that there seems to be no corresponding effect on the nitrogen shifts of secondary and tertiary piperidines. The ^{15}N-chemical shift of 2-aminoadamantane (**25**) is 3.2 ppm to lower field than that of *cis*-4-*tert*-butylcyclohexylamine (**23**) and this could be the result of



23

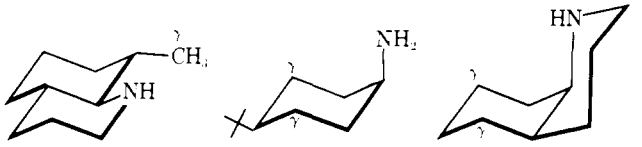


25

the expected effect. However, the anti γ-carbons of **25** are only shifted 1.2 ppm toward higher field compared with the parent adamantane.[14c]

In close analogy to ^{13}C-NMR, the ^{15}N resonances of piperidines are shifted upfield by gauche interactions with γ

substituents. The axial methyl-group effect on the nitrogen shift of *trans*-3,5-dimethylpiperidine (**3a** → **8a**) is *+10.3 ppm*. The +7.5 ppm change for the *N*-methyl derivatives (**3b** → **8b**) is likely to be the result of differences in the proportion of axial *N*-methyl for these compounds (as discussed above). The 8.9 ppm difference between the resonance signals of the epimeric 3-methylquinolizidines **21** and **22** shows the same influences as in ^{13}C NMR. The upfield shift per gauche interaction is also not very constant:[14b] the effect of the gauche γ-methyl group on the nitrogen shift of 8(e)-methyl-*trans*-decahydroquinoline (**17**a) is only +5.5 ppm and the upfield shift per interacting



17a **23** **16a**

methylene group is 5.3 ppm for *cis*-decahydroquinoline (**16a**) and 4.4 ppm for *cis*-4-*tert*-butylcyclohexylamine (**23**).

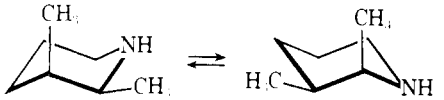
The γ-steric effect on ^{15}N chemical shifts is not restricted to interactions with alkyl groups. The shift difference between *cis*- and *trans*-1,2-diaminocyclobutane is 13.5 ppm,[2] and the γ-epoxy oxygen of scopolamine (**27**) causes an upfield shift of 21.5 ppm compared to atropine (**26**) (Table I).

The gross effect of the geminal γ-methyl groups in 3,3-dimethylpiperidine (**1a** → **11a**) is +6.3 and +4.8 ppm on *N*-methyl-3,3-dimethylpiperidine (**1b** → **11b**). Thus, the effect of γ-geminal CH_3 groups is −3.7 ppm.

δ-Substituent Effects. The influence of either equatorial or axial δ-methyl groups on the ^{15}N chemical shifts of piperidines, as seen from the changes: **1a** → **4b**, **1b** → **4b**, **1a** → **12a**, and **1b** → **12b** (Table I), are very small for both secondary and tertiary amines.

Use of Substituent Parameters. The substituent-shift parameters derived from the ^{15}N chemical shifts of a series of piperidines, related compounds, and their *N*-methyl derivatives measured in cyclohexane solutions are summarized in Table IV. There is clearly a parallelism with the corresponding carbon-shift parameters[14b] except for only the α^{eq}, α^{ax}, and the β^{ax} (α-CH_3) parameters. A similar set of shift parameters can be obtained using the shifts of Table I for methanol solutions.

Use of these parameters and the $^{15}N/^{13}C$ shift correlation for structural and conformational analysis can be illustrated by *cis*-2,3-dimethylpiperidine (**9a**). With this compound, ring inversion equilibrates two nonequivalent conformers, **9c** and **9d**. The calculated ^{15}N chemical shifts on the basis of Table IV are *328.8 ppm* for **9c** and *327.3 ppm* for **9d** which are both



9c **9d**

close to the experimental value of *329.9 ppm* and, of course, do not permit any conclusions about the position of the conformational equilibrium. More help is possible from the $^{15}N/^{13}C$ shift correlation for secondary piperidines in cyclohexane (Table II). Now we find that the observed nitrogen shift, *329.9 ppm*, lies between the shift obtained from the correlation line *332.6 ppm* (and the calculated carbon shift of the hydrocarbon analog of **9c**) and the shift of *327.3 ppm* from the correlation line (and the measured C3 shift of the 1:1-conformer mixture of *cis*-1,2-dimethylcyclohexane[14a]). This analysis and the preferred conformation of the closely related *cis*-decahydroquinoline, **16a**,[15] suggest that conformer **9c** of *cis*-2,3-dimethylpiperidine may be more stable than conformer **9d**, and indeed, a recent ^{13}C NMR study[23] suggests about a tenfold preference for conformer **9c** over **9a** at low temperatures.

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References and Notes

(1) (a) Supported by the Public Health Service, Research Grants No. GM-10224 and GM 11072, from the Division of General Medical Sciences, and by the National Science Foundation. (b) John Simon Guggenheim Fellow, 1975–1976.
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