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^{14}N AND ^{15}N NMR STUDIES OF HIGHLY STERICALLY HINDERED TERTIARY AMINES

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Abstract: ^{14}N/^{15}N NMR and molecular mechanics MM2 have been applied to study the structural changes in a series of highly sterically hindered amines. The NMR parameters, chemical shifts, ^{15}N-^{1}H coupling constants and the ^{14}N linewidths, are sensitive to the variations in sterical hindrance about the nitrogen. In particular, the chemical shift of the extremely hindered tri-isopropylamine (**4**) has been shown to deviate from the correlation calculated from the substitution parameters and from the correlation with the ^{13}C chemical shift of the corresponding hydrocarbon. These results are consistent with the results of a gas phase electron diffraction study which showed that **4** exhibits a trigonal planar structure.

Introduction

The effects of steric hindrance on the properties of organic molecules continue to attract the attention of researchers in a number of diverse areas. Sterically hindered amines have proved to be an interesting practical area of study because of their importance in organic synthesis and their diverse applications in industry.[1]

Theoretically, sterically hindered amines are particularly interesting because steric effects can be used to radically change the geometry about a nitrogen atom, and therefore greatly modify the chemical properties of the attached lone pair of electrons. Such effects on amine basicity in solution and in the gas phase are well known.[2] Similarly steric effects on NMR parameters have been observed and correlated with structural features in sterically hindered amines.[3-6]

For the most part, the sterically hindered amines which have been previously studied were only moderately strained and exhibited only modest effects due to steric hindrance. Recently we became interested in investigating the effects of extreme steric hindrance on amine groups.[1] In particular, we attempted to determine whether the normal pyramidal geometry of an amine could be deformed to a more planar structure due to steric interactions. Because this deformation would involve a geometric change about nitrogen, the hybridization about the nitrogen atom would be expected to change from the normal pyramidal sp^3 to a trigonal planar sp^2. The nitrogen lone pair in the latter case would be expected to exhibit significant "p-character". Such geometric and electronic changes would be expected to be reflected in changes in parameters observed in the nitrogen NMR of these compounds. We decided to investigate the ^{14}N and ^{15}N NMR properties of a series of tertiary amines (**1**-**4**), varying the nitrogen substituents in a way that steric interactions increased about the nitrogen atom, and observing the spectral changes resulting from the increased steric hindrance.

We were particularly interested in comparing the NMR properties of the moderately hindered amines diisopropylmethylamine (**1**), diisopropylethylamine (**2**) and di-tert-butylmethylamine (**3**) with the extremely hindered tri-isopropylamine (**4**). Recent investigations of the latter compound indicated that severe overcrowding due to steric effects does in fact lead to significant flattening of the normal pyramidal amine structure. Such flattening in **4** has been verified by gas-phase electron diffraction studies.[7]

Experimental Section

Di-isopropylethylamine (**2**) was obtained from Aldrich Chemicals. Amines **1** and **3** were prepared as described in the literature.[8] Tri-isopropylamine (**4**) was prepared by the method of Kuffner and Koechlin.[7, 9]

All NMR experiments were performed on a Bruker AMX-500 NMR spectrometer in a 5 mm broadband probe. The spectrometer frequencies are 50.8 MHz for ^{15}N and 36.2 MHz for ^{14}N. Samples were prepared in methanol (20%:80% by volume CD_3OD/CH_3OH). Some samples were also studied in $CDCl_3$. ^{15}N spectra were obtained either by regular decoupled spectrum or by using DEPT[10] with proton decoupling. Composite pulse decoupling, GARP,[11] was used for both experiments. The proton-coupled spectra of the amine hydrochlorides, from which $^1J_{^{15}N^1H}$ (abbreviated hereafter as J_{NH}) was determined, were obtained by DEPT without proton decoupling. ^{14}N spectra were obtained without proton decoupling. For both ^{15}N and ^{14}N, external samples of neat CH_3NO_2 was used as the reference. All spectra were obtained at 25° C.

There are several advantages of using ^{14}N NMR in addition to ^{15}N NMR. The sensitivity of ^{14}N NMR (natural abundance and the relaxation rate differences) is at least two orders of magnitude higher than that of ^{15}N NMR at natural abundance.[12] In addition, ^{14}N linewidth is a sensitive probe of the geometry and symmetry at the nitrogen site. The latter point will be elaborated in later sections.

Results

Chemical Shifts of Amines and Amine Hydrochlorides

For some samples, both ^{15}N and ^{14}N spectra were taken under identical experimental conditions. The resulting ^{15}N and ^{14}N chemical shifts (Table 1) usually agree with each other to within 0.5 ppm. Thus in subsequent discussions of the chemical shifts, these two chemical shifts will be used interchangeably and referred to as "nitrogen chemical shifts", except in discussions specifically related to a particular nucleus, *e. g.* the linewidths of the ^{14}N signals.

As it was observed in other amines and amine hydrochlorides, the nitrogen chemical shifts of amines lie uniformly downfield from those of the corresponding amine hydrochlorides.[3-5] The amine nitrogen chemical shifts in general change toward downfield for both amines and amine hydrochlorides when the alkyl group changes from methyl to ethyl, *i*-propyl and *t*-butyl as reported in the literature.[4,12,13] The exception observed in the present study is amine **4**, where an appreciable upfield shift was observed. No such anomaly was found in the amine hydrochloride of **4**.

Table 1. ^{15}N and ^{14}N Chemical Shifts of Amines and Amine Hydrochlorides (in ppm), ^{14}N Line Widths (Number in Hz in Parenthesis) in Methanol and $CDCl_3$ and J_{NH} (in Hz) of Amine Hydrochlorides in Methanol.[a]

Compound	Amine		Amine Hydrochloride			$\Delta(\delta)$[b]
	$\delta(^{14}N)$	$\delta(^{15}N)$	$\delta(^{14}N)$	$\delta(^{15}N)$	J_{NH}	
In Methanol						
Di-isopropyl methyl **1**	-329.5 (870)		-317.6 (205)	-317.2[c]	74.8	11.9
Di-isopropyl ethyl **2**	-320.2 (880)		-308.0 (138)	-307.8	74.8	12.2
Di-t-Butyl methyl **3**	-323 [d]			-305.2	72.3	17.8
Tri-isopropyl **4**	-327.5 (500)	-327.8	-302.3 (167)	-301.9	74.3	25.6
In Chloroform						
Di-isopropyl methyl **1**	-325.4 (800)		-314.8 (500)	-315.6		10.6
Di-isopropyl ethyl **2**	-318.2 (990)		-308.6 (450)			9.6
Di-t-Butyl Methyl **3**	-319.4 (1100)		-303.3 (610)	-304.2		16.1
Tri-isopropyl **4**	-328.8 (645)		-304.8 (320)			24.0

[a] Chemical shifts measured in ppm downfield from neat nitromethane. $\delta(^{15}N)$ is accurate to ± 0.1 ppm and $\delta(^{14}N)$ to ± 1 ppm. The ^{14}N linewidth is accurate to ± 5 Hz, and J_{NH} to ± 0.5 Hz.

[b] Difference in nitrogen chemical shift upon protonation, defined as $\Delta(\delta) = \delta(\text{amine hydrochloride}) - \delta(\text{amine})$.

[c] Also previously reported in Ref. 4.

[d] Linewidth not measured because of low signal to noise due to low concentration.

Empirical calculations of nitrogen chemical shifts have been made with substitution parameters in a similar way as that for ^{13}C.[4,13] Such calculations have been shown to reproduce the nitrogen chemical shifts of a large series of primary, secondary and tertiary amines and amine hydrochlorides.[4,13] We have compared the chemical shifts with those calculated from these substitution parameters for both the amines and hydrochlorides. The results are shown in Figure 1. It is clear that the correlations between the experimental and calculated shifts are excellent for all amine hydrochlorides in methanol. While there are larger differences between the calculated shifts and the observed shifts in $CDCl_3$, because the substitution parameters used were determined for methanol as the solvent, the linearity of the correlation is not affected (Fig. 1B). Similar agreement was found for all amines except for **4** (Fig. 1A), where a large deviation is evident.

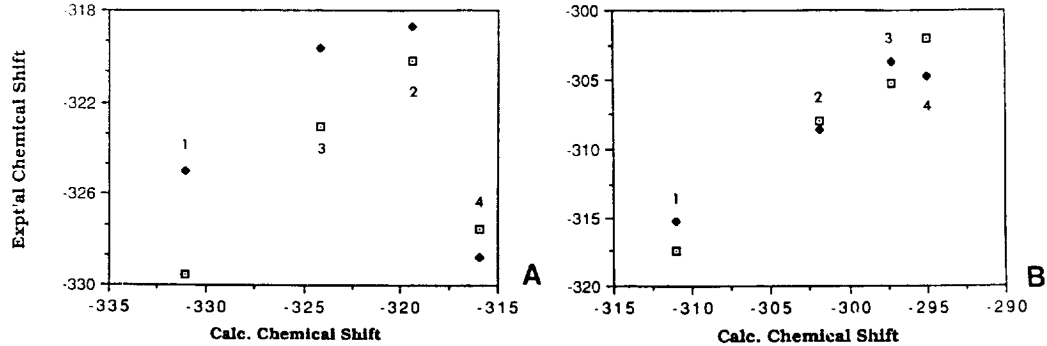


Figure 1. Experimental δ(^{15}N) of amines (A) and amine hydrochlorides (B) *vs* the calculated δ(^{15}N) (▣ in methanol and ◆ in $CDCl_3$)

It has been demonstrated that there is good linear correlation between the nitrogen chemical shift of amines and amine hydrochlorides with the ^{13}C chemical shift of the corresponding hydrocarbons.[4, 13] Such a comparison is made between the observed nitrogen shifts in the present study and the ^{13}C shifts of the corresponding hydrocarbons reported in the literature.[14] As shown in Figure 2, the linear correlation holds fairly well for the amine hydrochlorides but a significant departure from linearity occurs for **4**, in the similar manner as the departure that occurs in the correlation between calculated (from substitution parameters) and observed nitrogen shifts (see Figure 1). The origin of the deviation from linear correlation and the parallel between the comparisons shown in Figures 1 and 2 are clearly due to a significant change of the geometry of free amine **4**, which cause the chemical shift of **4** to deviate from the calculation based on substitution parameters derived from amines with little or no steric constraints. Thus the results from the present study are consistent with the conclusion by Bock *et al*[7] that **4** approaches a planar structure, while the other amines (**1-3**) have the normal pyramidal structure.

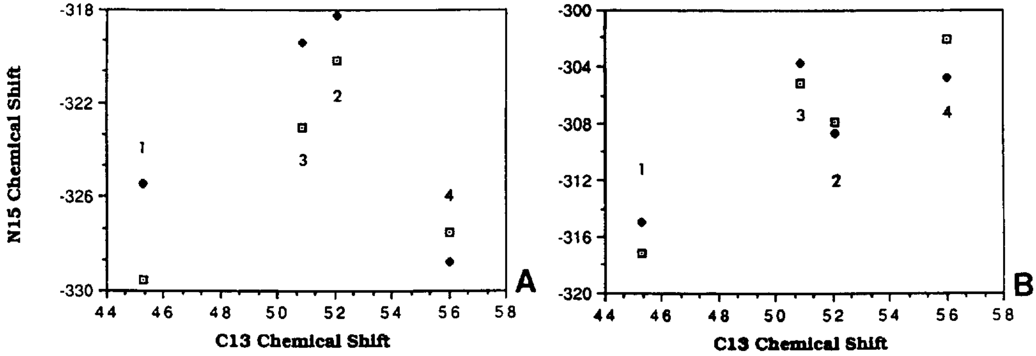


Figure 2. Experimental δ(^{15}N) of amines (A) and amine hydrochlorides (B) *vs* δ(^{13}C) of the corresponding hydrocarbons (▣ in methanol and ◆ in $CDCl_3$).

The differences in nitrogen chemical shifts between chloroform and hydrogen bonding MeOH are quite similar for **1-3**, probably indicating that the effects of hydrogen bonding on the nitrogen shift are similar for these three amines. It is, however, different for **4**. There appears to have less or no difference between shifts between the two solvents in the nitrogen shifts for the latter.

^{14}N signals of the amines are consistently broader than those of the corresponding amine hydrochlorides. In methanol, on the average the linewidth for the amines is about 500-900 Hz while that for the amine hydrochlorides is about 170 ± 30 Hz (Table 1). There are larger scatters in the linewidths in $CDCl_3$. The reason for this large difference in the linewidth between free amine and amine hydrochlorides is due to the near tetrahedral geometry of the hydrochlorides, which renders the ^{14}N quadrupolar coupling constant (qcc) substantially smaller than the qcc of the pyramidal amines (or near trigonal planar geometry of **4** as suggested by Bock *et al*[7]). According to this same criterion, the fact that the ^{14}N linewidth of the hydrochloride of **4** is similar to those of the other hydrochlorides, indicates that the near tetrahedral geometry is maintained for the hydrochloride of **4**. The fact that the ^{14}N linewidth for amine **4** (500 Hz in methanol and 645 Hz in $CDCl_3$) is appreciably smaller than those of **1-3** (*ca* .900 Hz) is probably due to the C_{3v} symmetry of **4**, and is unrelated to the change from pyramidal structure in **1-3** to near planar in **4**.

The change of the nitrogen chemical shift upon protonation, *i. e.* the difference between the chemical shifts of the hydrochloride and the corresponding amine ($\Delta(\delta)$ in Table 1) appears to closely parallel the increase in the strain energy of the amines.

J_{NH} of Amine Hydrochlorides

The J_{NH} for amine hydrochlorides **1-4** in MeOH are practically the same at *ca* 74 ± 1 Hz. The magnitude of the one-bond coupling is proportional to the s character of the nitrogen orbital participating in the N-H bond.[15] If the hydrochloride of **4** deviates significantly from tetrahedral symmetry and approaches near planarity as proposed for amine **4**, then the orbital for the N-H bond in **4** should be essentially a p-like orbital, with little s character. The near constancy of J_{NH} thus indicates that the hybridization of the nitrogen orbital involved in the N-H bond, and thus the geometry of the molecules, are essentially the same for all the amine hydrochlorides. This corroborates the results obtained from ^{14}N linewidths and chemical shift correlations.

MM2 Energy Computation

MM2 energy minimizations[16] were also carried out to qualitatively compare the strain of the hindered free amines and the corresponding ammonium salts with the observed nitrogen chemical shifts. Starting with the moderately strained di-isopropylmethyl amine, additional carbon substitution not unexpectedly lead to increased steric energy. It should be noted that of the isomeric hindered amines tri-isopropylamine (**4**) and di-*t*-butylamine (**3**), the former is more hindered. The difference is even more pronounced in the case of the corresponding hydrochlorides. This appears to be mainly due to much greater torsional distortion in tri-isopropylamine and its salt. The results are summarized in Table 2 in which various contributions to the total energy are presented.

It should also be noted that in each case except that of **4**, protonation decreases total strain rather significantly. In the case of **4**, protonation causes an increase in strain. As indicated in Table 2, this appears to be mainly due to a significant increase in the contribution to total strain from the "bending" term - - - deforming bond angles from their optimum values. This effect may be explained by a change in optimum bond angle from the trigonal tri-isopropylamine to the much more hindered tetrahedral geometry required for the corresponding ammonium salt. The presence of a "non-deformable" nitrogen to hydrogen bond as opposed to the "more deformable" nitrogen lone-pair leads to greater steric interactions in the salt. These interactions lead to a significant flattening about the ammonium nitrogen increasing total "bending" strain.

Table 2. MM2 Energies for Amines and Hydrochlorides **1-4** (in Kcal mol $^{-1}$).[a]

Compound	Total	Stretch	Bend	S/B	Torsion	1,4 vdW	Non 1,4 vdW
1	20.47	1.86	4.71	0.63	4.03	6.63	2.60
1.HCl	18.85	1.16	5.29	0.53	5.29	4.69	1.89
2	28.26	2.30	7.11	0.83	6.87	7.94	3.22
2.HCl	19.28	1.07	5.21	0.56	6.85	5.38	0.21
3	31.53	3.96	9.87	1.03	3.94	7.68	5.05
3.HCl	28.98	2.62	10.86	1.12	4.58	5.63	4.18
4	31.72	2.72	9.57	1.03	6.57	8.50	3.32
4.HCl	32.03	1.95	12.10	0.98	7.46	6.43	3.11

[a] S/B stands for stretch-bend interactions; vdW stands for van der Waals interactions. For a more complete description of the various terms included in this table, see Schnur *et al.*[17] The dipole term has been omitted from this table because its contributions are negligible in all cases.

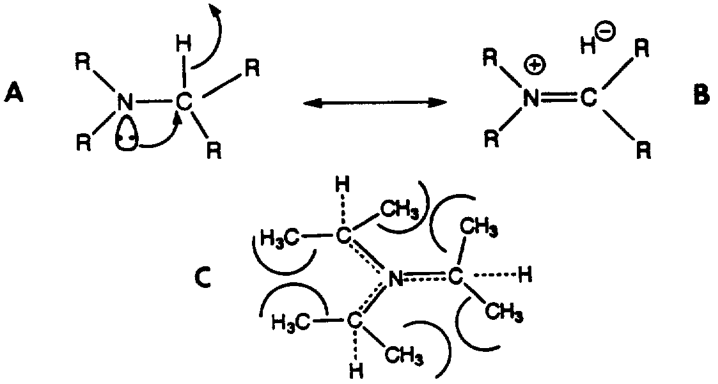
Discussion

In examining the nitrogen chemical shifts of previously reported tertiary amines,[4] it is apparent that both inductive and steric effects play important roles in determining the observed peak positions. Analogous to the treatment of secondary amines by Warren and Roberts[18] we compared the nitrogen chemical shifts observed by successive replacement of the hydrogen atoms of trimethylamine by methyl groups. Initial single replacement of hydrogens (α substitution) leads to successive downfield shifts of 12, 12, and 10 ppm in going from trimethylamine to ethyldimethylamine to diethylmethylamine to triethylamine. Further substitutions on the carbons directly attached to the nitrogen atom (α') lead to a significantly lessened downfield increment of 2-4 ppm. For example, the difference in chemical shift between ethyldimethylamine to isopropyldimethylamine is 2 ppm, that between diethylmethylamine to di-isopropylmethylamine is 7 ppm. A third successive replacement of hydrogen on a carbon directly attached to the nitrogen atom (α") also generally leads to a small downfield shift of 4 ppm. All of the sterically hindered tertiary amines in our study show shifts consistent with these values except for **4** which shows a considerable deviation from the calculated values. Incremental α and α' substitution of **1** or α' substitution of **2** would lead to a predicted nitrogen chemical shift of approximately -315 ppm. The observed value is about -329 ppm. Clearly steric factors strongly influence the observed chemical shift in **4**.

A comparison of the changes in the nitrogen chemical shifts observed upon protonation of the hindered tertiary amines also indicates the unusual behavior of **4**. Protonation of relatively unhindered tertiary amines leads to downfield shift of 9 - 12 ppm. Slight increases in these downfield shifts are observed in the more hindered **3**, while these downfield shifts are approximately 24 ppm for **4**, significantly larger than those observed for the moderately hindered amine protonation. It should be noted that upon protonation, the resulting tri-isopropylammonium species does not deviate from the expected increased downfield shift observed with increased steric hindrance.

How can severe steric effects bring about unusual changes in the observed nitrogen chemical shifts in the case of tri-isopropylamine and its ammonium salt? A number of possibilities might explain this phenomenon. In contrast to all-carbon systems in which non-bonded interactions produce upfield shifts in the ^{13}C spectra, similar non-bonded interactions lead to downfield shifts in the nitrogen NMR spectra of tertiary amines. This has been explained by the "added degree of flexibility through bond angle or conformational changes so as to minimize the effect of non-bonded interactions on their ^{15}N shifts".[4] The likely source of this increased flexibility is the rapid nitrogen inversion which occurs in amines. The flattening observed in tri-isopropylamine would decrease this flexibility, leading to an upfield shift such as that observed in the all-carbon systems. Protonation of **4** would lead to the tetrahedral geometry typical of normal ammonium salts, preventing this anomalous behavior.

An alternative explanation might involve stereoelectric factors. As shown in **Scheme 1**, hyperconjunctive effects can occur between the lone pair of electrons on nitrogen and hydrogen atoms on the carbon atoms directly attached to this nitrogen (the α carbon). All of the tertiary amines investigated in this study have this structural feature. The increased positive charge on the nitrogen atom in resonance contributor B should lead to a downfield shift in the nitrogen signal. Geometrically, such a resonance contribution would tend to flatten the substituents on carbon, while lengthening the carbon hydrogen bond parallel to the lone pair. In the case of a planar tri-isopropylamine such a flattening of the substituents might be geometrically unfavorable, leading to severe steric interactions between the methyl groups on adjacent isopropyl groups as shown in structure C.



Scheme 1

In summary, the nitrogen NMR parameters, chemical shifts, ^{14}N linewidths and J_{NH}, are sensitive to the effects of steric hindrance around the nitrogen atom among the highly strained tertiary amines studied. In particular, the unusual behavior of **4** as compared with the less strained amines corroborates the gas phase electron diffraction results[7] which indicate that the structure of **4** is trigonal planar.

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