Nuclear Magnetic Resonance Spectra of Amines I. Identification of *N*-Methyl Tertiary Amines

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The effects of strongly acidic solvents on the chemical shift and spin-spin splitting of the methyl protons in *N*-methyl tertiary amines are found to be unique for this particular functional group. These effects provide the basis for the simultaneous identification of the *N*-methyl group and the tertiary amine structure in compounds of unknown structure.

AN ANALYTICAL method using NMR has been developed for the qualitative analysis of the tertiary *N*-methyl amine function. The method is specific for aliphatic tertiary *N*-methyl amines and also distinguishes aliphatic from aromatic compounds. The method is based upon the effects of strongly acidic solvents on the NMR spectra of tertiary *N*-methyl amines.

The dependence of the NMR spectrum of *N*-methyl groups on hydrogen-ion concentration and the proton exchange rate in aqueous solutions is well known. Loewenstein and Meiboom (1) have made an extensive study of methylamine, dimethylamine, and trimethylamine in this regard. The splitting of the NMR absorption band of the methyl group in methylamine into a quartet by the 3 protons in the adjacent primary amine ion has likewise been studied and reported by Jackman (2) and Pople, Schneider, and Bernstein (3).

In this investigation the effects of protonation of the nitrogen atom and subsequent splitting of the *N*-methyl protons in aliphatic tertiary amines are illustrated. The NMR spectral changes are recommended for rapid identification of this class of amine.

EXPERIMENTAL

All spectra were recorded on a Varian A-60 spectrometer using Varian sample tubes. Deuterated chloroform and trifluoroacetic acid were used as solvents. Concentrated reagent sulfuric acid was used for diamine and aromatic amines. The spectra were obtained on samples at room temperature at a concentration of 50 mg./ml.

The simple tertiary amines were Eastman Organic Chemicals as purchased from Distillation Products Industries, Rochester, N. Y. The chlorpromazine base was analytical standard grade.

RESULTS AND DISCUSSION

Tertiary aliphatic amines containing 1 or more *N*-methyl groups show nuclear magnetic resonance (NMR) absorption of the methyl protons as a single peak in the vicinity of 2.2 p.p.m. downfield from tetramethylsilane as reported by Jackman (2). This single peak is characteristic of *N*-methyl tertiary amines as free base. The 2.2-p.p.m. chemical shift occurs in solvents of low dielectric constant, *e.g.*, carbon tetrachloride and chloroform. In a strongly acidic solvent such as trifluoroacetic acid the amine is transformed into the tertiary amine ion. The positive electrostatic charge on the ion increases the *N*-methyl chemical shift approximately 1 p.p.m. and the single peak is split into a doublet with a coupling constant of 5 to 6 c.p.s.

Figure 1 illustrates the NMR spectrum of an *N*-methyl tertiary amine as free amine in deuterated chloroform (spectrum A), and as the tertiary amine ion in trifluoroacetic acid (spectrum B). This phenomenon is seldom observed for an amine salt in chloroform solution due to the poor NMR spectrum resolution of ion dipoles and other ion aggregates in solvents of low dielectric constants. Solvents of medium to high dielectric constant such as water, methanol, or trifluoroacetic acid are preferred for high resolution spectra of amine salts.

The splitting of the methyl absorption band observed in trifluoroacetic acid solution is due to coupling of the methyl protons with the proton bound to the nitrogen in the tetrahedral tertiary amine ion. As mentioned previously in this paper, a similar effect has been observed in the case of primary amines. The protons adjacent to the NH_3^+ ion are split into a quartet (2, 3).

The observations from spectra A and B are general for *N*-methyl aliphatic tertiary amines. Table I lists the *N*-methyl chemical shift data for the NMR spectra of 8 *N*-methyl aliphatic amines and

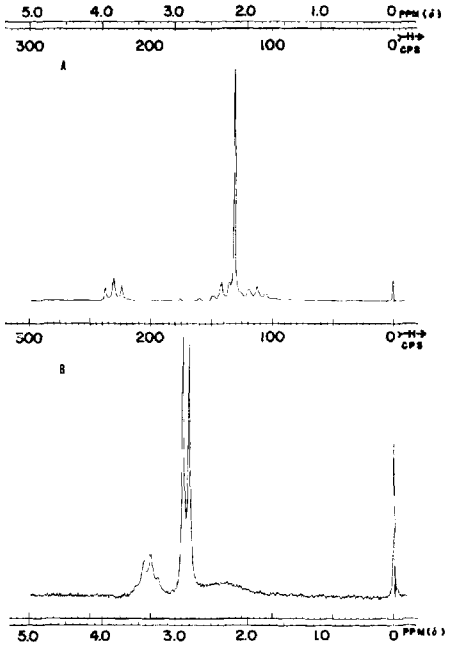

Fig. 1.—NMR spectrum of chlorpromazine (A) in $CDCl_3$ (B) in CF_3COOH.

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TABLE I.—NMR CHEMICAL SHIFTS FOR *N*-METHYL GROUP IN ALIPHATIC TERTIARY AMINES

Compd.	δ^a in $CDCl_3$, p.p.m.	δ^a in CF_3COOH, p.p.m.	J^b in CF_3COOH, c.p.s.
Trimethylamine	2.20	3.01	5.5
2-Dimethylaminoethanol	2.28	3.02	5.0
n-Dodecyldimethylamine	2.25	3.06	5.5
N-Methyldioctadecylamine	2.18	3.05	5.5
N-Methylpiperidine	2.22	3.01	5.5
N-Dimethylcyclohexylamine	2.32	3.03	5.5
N,N-Dimethylbenzylamine	2.22	3.05	5.5
10-(3-Dimethylaminopropyl)-2-chlorophenothiazine (chlorpromazine)	2.17	2.84	5.5

[a] δ = chemical shift downfield from tetramethylsilane internal standard. [b] J = coupling constant between proton on nitrogen and protons on adjacent methyl.

TABLE II.—NMR CHEMICAL SHIFTS FOR TERTIARY *N*-METHYL GROUPS IN AROMATIC AMINES AND ALIPHATIC DIAMINES

Compd.	δ in $CDCl_3$	δ in CF_3COOH	J in CF_3COOH	δ in H_2SO_4	J in H_2SO_4
N,N-Dimethylaniline	2.83	3.42	0	3.41	5.0
N-Methyldiphenylamine	3.27	3.90	0	3.80	5.0
N-Methylpiperazine	2.22	3.21	0	3.09	5.5
N,N-Dimethylpiperazine	2.28	3.22	0	3.07	5.0

corresponding amine ions. Aromatic amines and aliphatic diamines generally require a stronger acid (*e.g.*, sulfuric) to split the methyl absorption (Table II). In sulfuric acid the ion is stable. These weaker amines exchange protons in CF_3COOH at a high enough rate to effectively decouple the ion proton (NH^+) resulting in a J constant of zero. The larger chemical shift due to ring currents in aromatic amines can be used to differentiate an aliphatic *N*-methyl amine from an aromatic amine.

The splitting has been observed for every *N*-methyl aliphatic tertiary amine examined to date at room temperature in trifluoroacetic acid. The amine must be added to the trifluoroacetic acid as the free base. If an amine salt of a strong inorganic acid such as amine hydrochloride is dissolved in trifluoroacetic acid, the amine ion-strong acid dipole remains unionized in the acid. The NMR spectrum in this case is usually too poorly resolved to allow one to observe the 5 to 6 c.p.s. splitting.

Chloroform and trifluoroacetic acid are much more widely useful as solvents for NMR than are either acidic or basic water, since many large tertiary amines and their salts are poorly soluble in either aqueous acid or base.

CONCLUSION

The differences between tertiary amine free base NMR spectra and tertiary amine ion spectra are an extremely useful diagnostic tool. The increased chemical shift and splitting of the *N*-methyl peak in the case of the ion makes it possible to establish the presence of the *N*-methyl group and aliphatic tertiary amine structure in compounds of unknown structure.

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