Pakistan J. Sci. Ind. Res., Vol. 15, Nos. 1–2, February–April 1972

COMPARATIVE STUDIES OF CHEMICAL SHIFT AND THE SOLVENTS EFFECT OF THE N-METHYL GROUPS BY NMR SPECTROSCOPY

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(Received February 16, 1971; revised May 1, 1971)

Abstract. NMR spectrometer has been used for the characterisation of *N*-methyl groups. The method depends on the decreased shielding of *N*-methyl protons. The decreased shielding results in a downfield shift of the *N*-methyl resonance, depending upon the type of compounds. Experimental evidences show *N*-methyl variations from 1.88 to 4.10 p.p.m.

Solvent shifts of *N*-methyl groups have also been studied and variations have been found both in aromatic and nonaromatic solvents. In aromatic solvents such as pyridine and benzene, the range of solvent shift varies from 0.03 to 0.85 p.p.m. In nonaromatic solvents, variation is not more than 0.20 p.p.m. Solvent shifts in deutero mixture of (a) chloroform and pyridine, (b) chloroform and benzene, (c) chloroform and dimethyl sulfoxide, have also been studied and interesting results were obtained.

The principal application of chemical shift of proton is a form of functional group analysis. Signals due to protons of methyl groups have come to assume a special importance in practical NMR spectroscopy, because they are strong, usually show first order splitting patterns and can be influenced by only one group in the α-proton (noncyclic carbon atoms).

A valuable collection of chemical shifts data for *N*-methyl groups is given by Ma and Warnhoff.[1] Characterisation of *N*-methyl groups in organic compounds[2] and the identification of different amines in acidic conditions have also been reported by various workers.[3,4]

Bible[5] has mentioned that the *N*-methyl groups appeared between 2.16–3.33 p.p.m. A wide range of *N*-methyl compounds has, therefore, been studied by NMR in an attempt to establish the maximum possible range of *N*-methyl groups.

In conjunction with the investigation of chemical shift, solvents effect have also been considered. In particular, the change in chemical shift commonly observed when the NMR of the same spectra are recorded using the same internal reference, but a different solvent is referred as 'solvent shift' and arises principally from the formation of collision-complex between the solvent and the solute.

Advantage is sometimes taken of the 'solvent shift' to remove the overlap of the absorption band and thus to aid the interpretation of the spectrum. Different deutero solvents, including aromatic solvents like pyridine and benzene, were used to study the solvent shifts of the various compounds. Solvent shifts of the order of 0.50 p.p.m. have often been reported when pyridine was taken as solvent.[6] In the present investigation, the following mixtures of deutero solvents, i.e. (i) chloroform+dimethyl sulfoxide, (ii) chloroform+pyridine and (iii) chloroform+benzene were taken under consideration.

Experimental

Solvents. Tetramethylsilane (TMS) spectroscopically pure for calibration purposes and used as an internal solvent; deuterochloroform (spectro-grade); deuterodimethyl sulfoxide (spectro-grade); deuteropyridine (spectro-grade); deuterobenzene (spectrograde); carbon tetrachloride (spectroscopically pure, E. Merck).

Compounds. Most of the compounds investigated, were of spectro-grade while others were research samples kindly supplied by Dr. D.M.W. Anderson, Department of Chemistry, University of Edinburgh, Dr. A. Kamal, P.C.S.I.R. Laboratories, Karachi and Dr. S. Siddiqui, Postgraduate Institute of Chemistry, University of Karachi. All are listed in Table 1 for which satisfactory elemental analyses existed.

Table 1. NMR Chemical Shift δ (p.p.m.) for *N*-methyl Groups in Deuterochloroform ($CDCl_3$) Solvent.

Compound	$-NCH_3$	$-OCH_3$	$-CCH_3$
N-Methylacetanilide	3.30	1.85	
p-Dimethylaminobenzaldehyde	3.07		
Dimethyl yellow dimethylaniline	3.09		
Michler's ketone	3.08		
p-Nitrosodimethylaniline	3.21		
Caffeine	3.41		
	3.59		
	4.10		
Gramine	2.35		
Nicotine	2.18		
N-Methylisatin	3.28		
5-Bromo-*N*-methylisatin	3.27		
N,*N*-Dimethylformamide	2.88		
	2.97		
Methylephidrine	2.35	0.98	
N-Methyl-3-chloro-6-nitroaniline	3.33		
	3.41		
Atropine	2.23		
N-Methylaniline	2.66		
N,*N*-Dimethyl-*p*-toluidine	2.88		2.29
N-Methyl-*N*-nitrosotoluene-*p*-sulphonamide	2.65		2.35
Cocanium hydrochloride	3.83		
Ajmaline	2.82		
Diacetylajmaline	2.83	2.14	
		2.25	
Protopine	1.92		
Cryptopine	1.88	3.86	

Procedure. The NMR spectra of each compound was obtained by using DP-60, NMR spectrometer of Varian Associates, Switzerland. In each case, 10–30 mg of the specimen in spectro-grade solvents were prepared with the inclusion of two to three drops of tetramethylsilane (TMS), which was used as an internal reference. Measurements were carried out in terms of the frequency independent unit δ p.p.m. with respect to TMS.

Discussion

During our study in the series of compounds in deuterochloroform as listed in Table 1, it was found that for different compounds, the range of *N*-methyl absorption varied from 1.88 to 4.10 p.p.m. as compared[5] to 2.16–3.33 p.p.m. Spectra of some of the compounds are shown in Fig. 1.

NMR spectroscopy undoubtedly is a useful and better method for detecting *N*-methyl group but sometimes it is very difficult to assign the position of *N*-methyl group, as several types of methyl give rise to unsplit 3-hydrogen NMR peaks and their rather broad ranges of absorption overlap considerably.

Solvent shifts of *N*-methyl group have also been studied and found that in different deutero solvents i.e. chloroform, carbon tetrachloride and dimethyl sulfoxide, the variation of solvent shifts have not been found more than 0.20 p.p.m., whereas in aromatic solvents such as pyridine and benzene, the commonly encountered range of magnitude of solvent shifts varied from 0.03 to 0.85 p.p.m. as shown in Table 2. It was expected that resonance frequencies from samples dissolved in pyridine would be uniformly shifted from those ordinarily observed in chloroform due to the different magnetic susceptibilities of the solvent.[7] When the spectra of different compounds in deutero-chloroform and pyridine were compared, marked differences in values appeared. Some of the lines in pyridine solvent shifted much more than others. It seemed that the pyridine preferred certain sites for coordination and the large shifts were due to the anisotropy associated with the ring current effect.[8] It was also found that the peaks, which were slightly superimposed in deuterochloroform, again reappeared in pyridine.

During our investigation, *N,N*-dimethylformamide, *p*-dimethylaminobenzaldehyde and *N*-methylformamide have shown some interesting results which require extra discussion.

N,N-*Dimethylformamide.* The NMR spectrum of DMF in deuterochloroform consists of two narrow doublets for the methyl group and an unresolved band of CH proton. The main splitting of methyl groups is due to partial double-bond character of the CN bond which introduces a barrier to free rotation at room temperature, forces one methyl group to remain closer to oxygen than the other.

Detailed study of these shifts of diamagnetic anisotropy of the aromatic nucleus (benzene as solvent) led to the conclusion that in the collision complex, the amide molecule is situated above the ring with partially positive nitrogen atom close to the ring and the partially negative oxygen away from it. The effect is reduced by all substituents on the benzene ring, particularly by electron with drawing groups. It was also found that the interaction of amide in *N,N*-dimethylformamide with pyridine appeared to be different from that with benzene since the former causes downfield shift of the absorption of both groups of *N*-methyl protons.

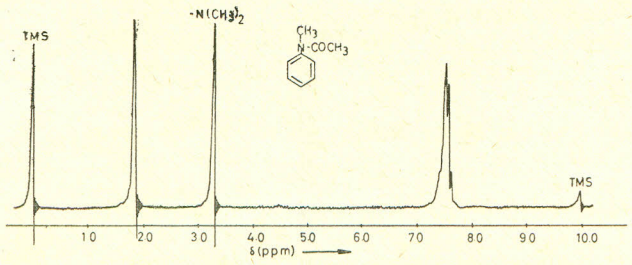
p-*Dimethylaminobenzaldehyde.* This compound has also been studied in different solvents and their mix tures. The results are shown in Table 2 and 3. The aromatic protons of *p*-dimethylaminobenzaldehyde might be called an A_2X_2 or A_2B_2 system, a system to indicate in which each proton in one group is not coupled equally to each and every proton in the second group Thus *p*-dimethylaminobenzaldehyde will be designated as an $A_2^1X_2^1$ system rather than an $A_2^1B_2^1$ type from examining the spectrum.

N-*Methylformamide.* The NMR spectrum of *N*-methylformamide in deuterochloroform consists of a single unresolved line for CH, an undefined quarduplet for NH and a narrow doublet for NCH_3. This spectra was slightly different from the spectra reported by earlier workers.[9]

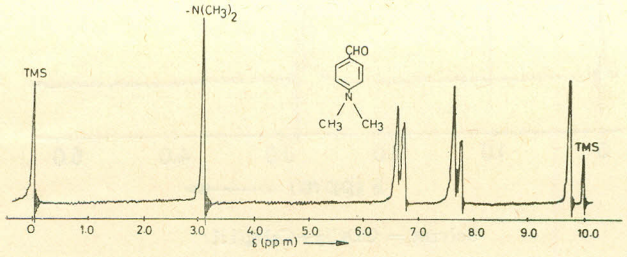
More interesting results are obtained when the compounds were taken in the mixtures of deutero solvents, i.e. (a) chloroform and dimethyl sulfoxide, (b) chloroform and pyridine, (c) chloroform and benzene (Table 3). Well-defined spectra were observed in the above-mentioned mixtures, but an in-

TABLE 2. NMR POSITIONS AND THEIR CHEMICAL SHIFT DIFFERENCES IN DIFFERENT DEUTERO SOLVENTS.

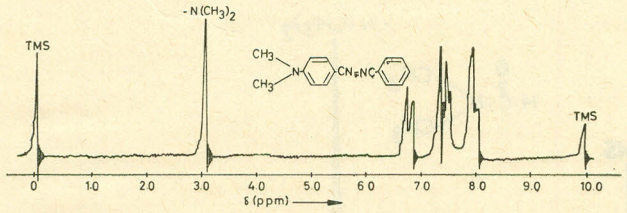
Compound	—NCH_3 in δ p.p.m.				
	$CDCl_3$	CCl_4	DMSO	C_5D_5N	C_6D_6
N-Methylacetanilide	3.30	3.25	3.28	3.47	3.15
p-Dimethylaminobenzaldehyde	3.04	3.04	3.07	3.00	2.41
Dimethyl yellow dimethylaniline	3.08	3.09	3.06	3.05	2.44
Michler's ketone	3.09	3.09	3.10	2.95	2.46
p-Nitrosodimethylaniline	3.21	Insol	3.20	3.09	Insol
N,N-Dimethylformamide	2.88	2.88	2.68	2.81	2.58
	2.97	2.97	2.80	2.87	2.74
N-Methylisatin	3.28	Insol	3.17	3.06	3.02
5-Bromo-*N*-methylisatin	3.27	Insol	3.22	3.20	2.43



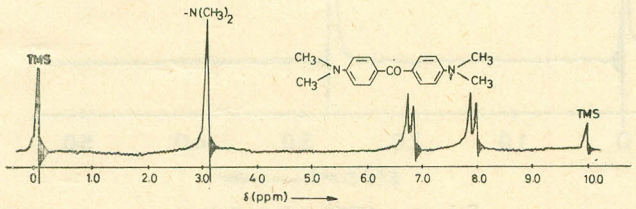
N-Methylacetanilide



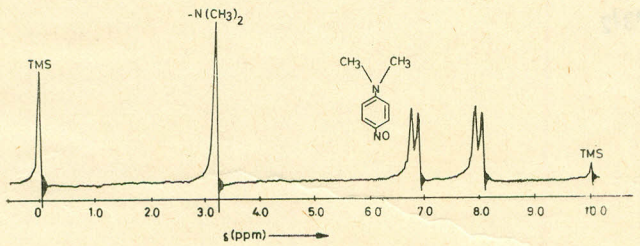
p-Dimethylaminobenzaldehyde



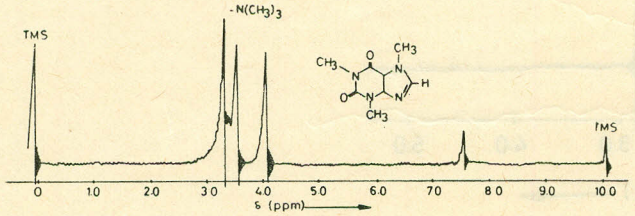
Dimethyl yellow dimethyl aniline



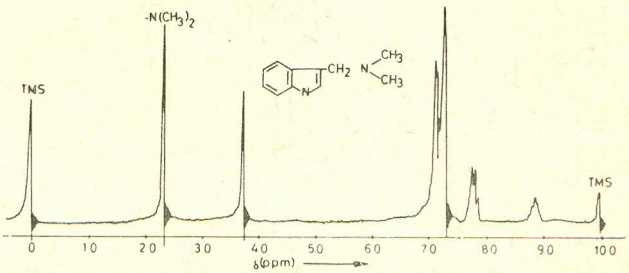
Michler's ketone



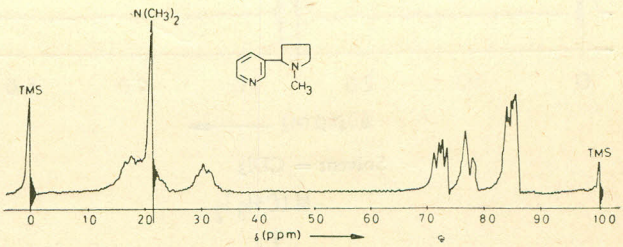
p-Nitrosodimethyl aniline



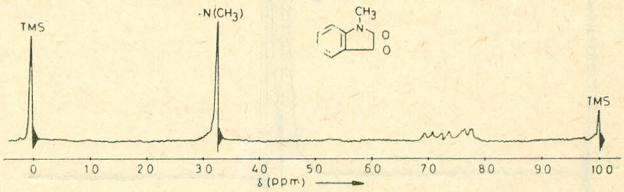
Caffeine



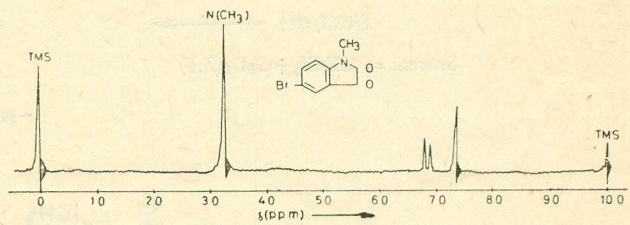
Gramine



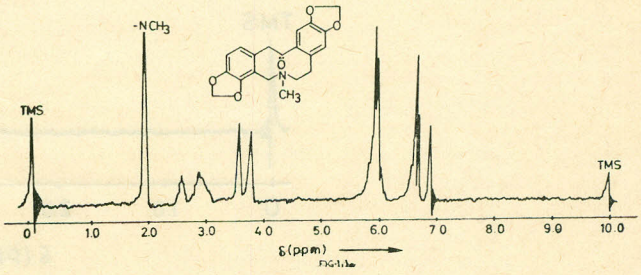
Nicotine



N-Methylisatin

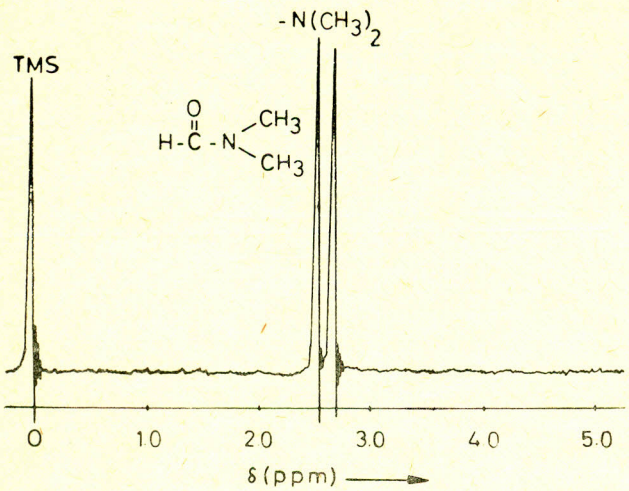


5-Bromo-*N*-methylisatin

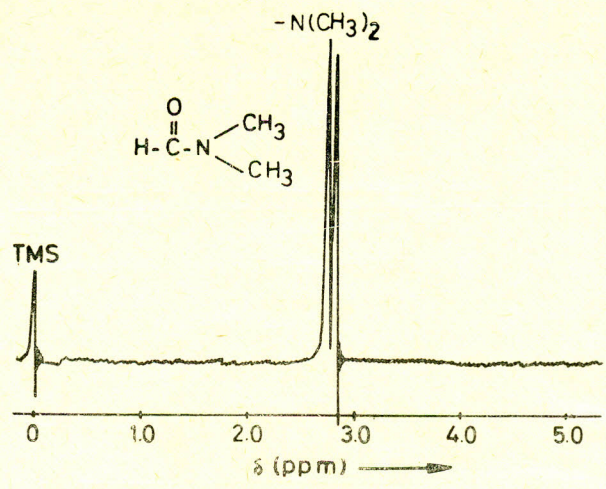


Protopine

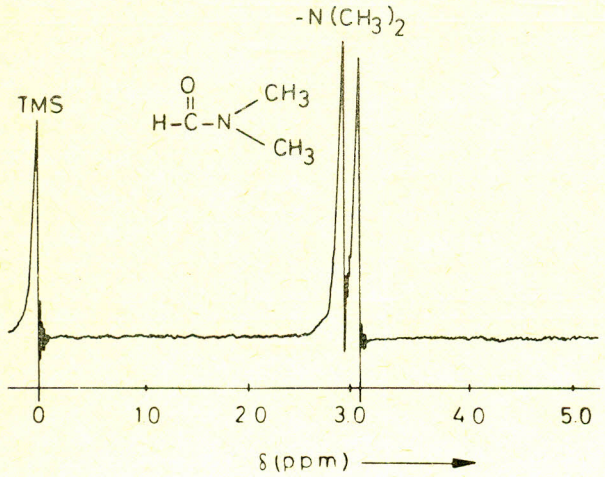
Fig. 1. Structures of the compounds mentioned in Table 1.



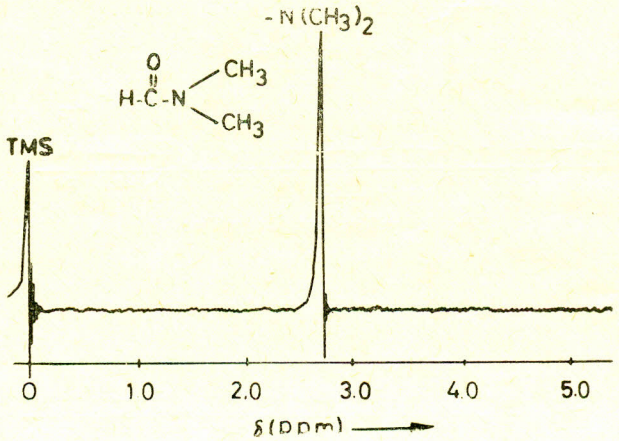
Solvent = CDl_3



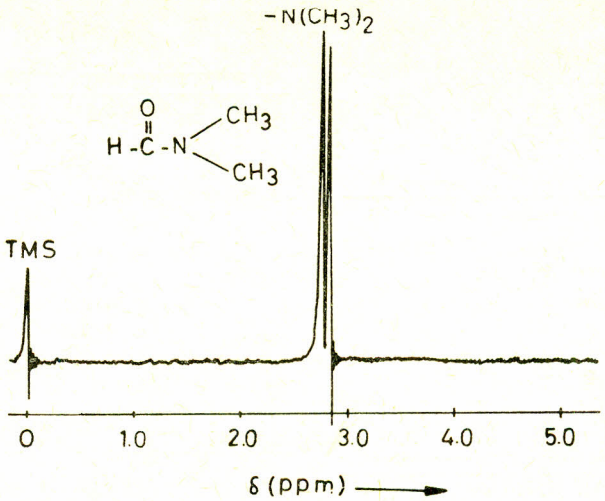
Solvent = $CDCl_3+C_6D_6(1:1)$



Solvent = $CDCl_3+C_6D_6(2:1)$



Solvent = $CDCl_3+C_6D_6(1:2)$



Solvent = C_6D_6

Fig. 2. NMR spectra of *N*,*N*-dimethylformamide in deutero mixtures.

TABLE 3. NMR CHEMICAL SHIFTS δ p.p.m. FOR *N*-METHYL GROUPS IN DIFFERENT MIXTURES OF DEUTERO SOLVENTS.

Compounds	—NCH_3 in δ p.p.m.		
	$CDCl_3$+DMSO	$CDCl_3+C_5D_5N$	$CDCl_3+C_6D_6$
N,*N*-Dimethylformamide			2:1 *ratio*
	2.91	2.86	2.79
	3.05	2.94	2.86 Doublet
			1:1 *ratio*
			2.73 Singlet
			1:2 *ratio*
			2.79 Doublet
			2.86
N-Methylacetanilide	3.31	3.31	3.31
p-Dimethylaminobenzaldehyde	3.04	2.96	2.80
Dimethyl yellow	3.09	2.95	2.62
Michler's ketone	3.05	2.95	2.87

teresting result was found when *N*,*N*-dimethylformamide was studied in the mixture of chloroform and benzene in the ratio of 1:1. The doublet of *N*-methyl in DMF collapses into a single sharp peak and the δ value was noted as 2.73; taking TMS as zero. When the NMR of *N*,*N*-dimethylformamide was studied in the same mixtures in the ratio of 2:1, two narrow doublets reappeared again but the absorption of both groups of *N*-methyl protons slightly shrank (Fig. 2). No such type of effect was encountered in other compounds.

Examples are sighted when the spectrum of the mixture of two steroids[10] was changed from deuterochloroform to pyridine as a solvent, the different methyl proton signals were shown as doublet, appeared as singlet.

The manner in which these changes occurred, are not fully described here. Their confirmation and possibilities will await further work which is in progress.

Acknowledgement. Thanks are due to Dr. D.M.W. Anderson, Department of Chemistry, University of Edinburgh, for providing the research samples.

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