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Dedicated to Professor Ionel Haiduc
on the occasion of his 65th birthday

SOLVENT EFFECTS IN ^{1}H NMR SPECTRUM OF 3-FORMYL-10-METHYL-PHENOTHIAZINE

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ABSTRACT. High resolution NMR spectra were recorded in order to assign the spin-spin couplings pattern of aromatic protons in the 3-formyl-10-methyl-phenothiazine structure. The effect of non polar [D]-chloroform, polar [D$_6$]-DMSO and magnetically anisotropic [D$_6$]-benzene solvents upon the chemical shifts of the 3-formyl-10-methyl-phenothiazine protons are discussed.

INTRODUCTION

The structure of 3-formyl-10-methyl-phenothiazine [1,2] was completely assigned using the 400 MHz ^{1}H NMR spectrum, the ^{13}C NMR spectrum together with the DEPT experiment spectrum and the two-dimensional homonuclear (H-H-COSY) and heteronuclear (HMQC and HMBC) experiments spectra.

The registered 2D H-H-COSY spectrum and the registered 2D HMQC spectrum of 3-formyl-10-methyl-phenothiazine are presented in the figure 1 together with the assignments of the protons and the carbon atoms.

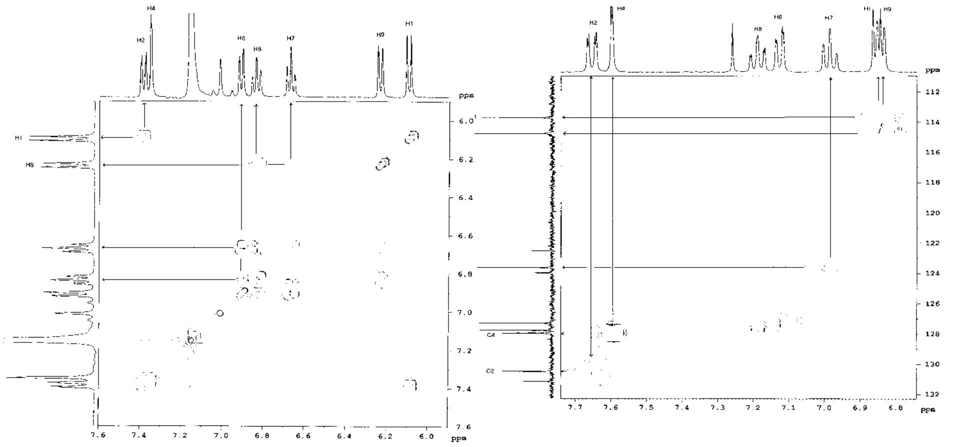

Fig. 1. 400 MHz spectra of 3-formyl-10-methyl-phenothiazine
a) 2D H-H-COSY spectrum in [D$_6$]-benzene solvent. b) 2D HMQC spectrum in [D]-chloroform.

The examination of the cross peaks presented in figure 1a., shows the couplings between vicinal protons and also the long distance *meta* protons couplings (*orto* coupling constants ^3J values are approximately 8 Hz and *meta* coupling constants ^4J are approximately 1.4 Hz). The correlation between the already assigned protons and the carbon atoms, shown by the cross peaks in the HMQC spectrum presented in figure 1b. made possible the assignment of all the tertiary carbon atoms. The 2D HMBC spectrum was used in quaternary carbon atoms assignments.

RESULTS AND DISCUSSIONS

The 400 MHz ^1H NMR spectrum of 3-formyl-10-methyl-phenothiazine was recorded in: non polar [D]-chloroform, polar [D$_6$]-DMSO and magnetically anisotropic [D$_6$]-benzene solvents. The interaction between these solvents and 3-formyl-10-methyl-phenothiazine determined the shifts of the aromatic protons signals as shown in figure 2.

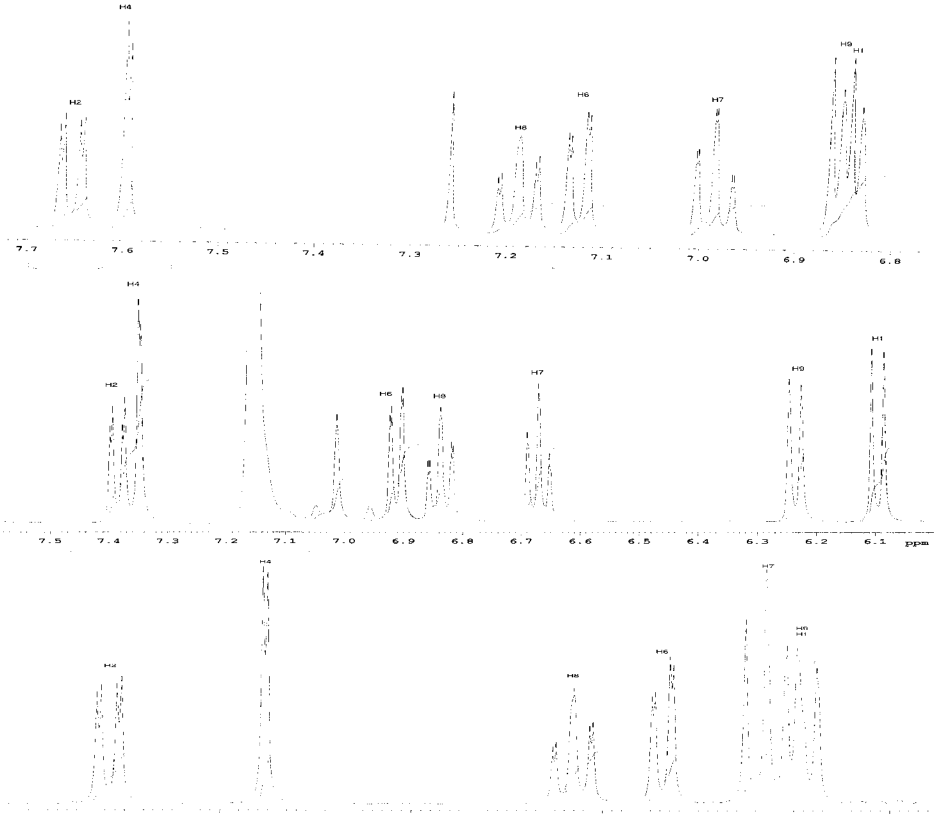

Figure 2. 400 MHz ^1H NMR spectra of 3-formyl-10-methyl-phenothiazine in: 1). [D]-CHCl$_3$; 2). [D$_6$]-C$_6$H$_6$; 3). [D$_6$]-DMSO

The greater chemical shift values for all the aromatic protons of the studied structure were recorded in the polar DMSO solvent, a fact that might be explained by donor-acceptor relation between the phenothiazine electrono-donor nucleus and the electrono-acceptor DMSO molecules. The less affected chemical shifts were those of protons labeled H_2 and H_4 strongly influenced by the electron withdrawing formyl group situated in their neighborhood.

The magnetic anisotropy of the formyl neighboring group determined the shielding of the H_4 signals as compared to the H_2 signals position, possibly due to a preferential conformation of the structure with respect to the attached formyl group in conjugation with the aromatic nucleus. In figure 3 we describe the spatial anisotropy of the carbonyl double bond, which determined the increased shielding zone near the H_4 proton. As seen in the figure, only a cisoid arrangement of the C=O–C=O system can explain the relative shielding of H_4 and the deshielding of H_2. As the heterocyclic S-atom is expected to experience a slight electron deficit (due to the combined action of the N atom and of the formyl group) this conformation leads to a minimization of the dipolar moment in the α form, as compared to the β form.

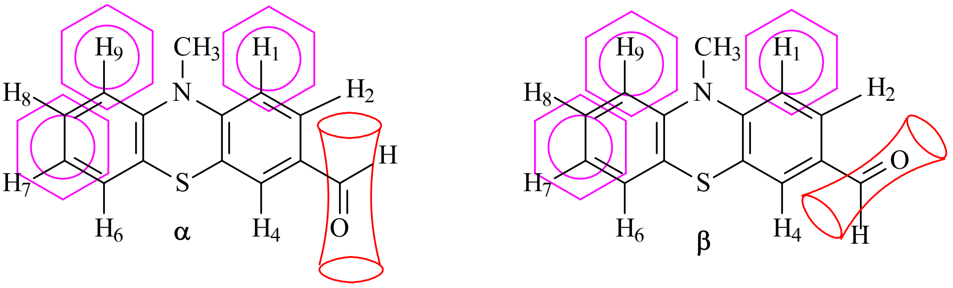

Figure 3. Shielding contributions due to the magnetic anisotropy of carbonyl double bond and benzene solvent molecules.

The interaction between the phenothiazine dissolved molecules and benzene solvent determined the shielding of all phenothiazine protons signals, due to a face to face orientation of the aromatic rings; thus, the phenothiazine protons were situated in the zone of increased shielding due to the induced *ring current* of the benzene nucleus. In figure 3 we described the possible spatial distribution of the benzene molecules, which determined the differenticlly increased shielding zones around the phenothiazine aromatic protons.

CONCLUSIONS

As it can be seen in table 1, which summarizes the recorded chemical shifts for the protons of the 3-formyl-10-methyl-phenothiazine structure in [D]-chloroform, [D_6]-DMSO and [D_6]-benzene solvents, the polar DMSO solvent induced the greater chemical shifts, and in the mean time, an ASIS effect of benzene solvent determined the smaller induced values. Both the preferred conformation of the formyl group, and the spatial interactions with benzene rings thus determined could give better insights for interpreting drug-receptor relationships in the phenothiazine class.

Table 1.

Chemical shifts for 3-formyl-10-methyl-phenothiazine protons in [D]-chloroform, [D_6]-DMSO and [D_6]-benzene solvents

δ(ppm)	CHO	H_2	H_4	H_8	H_6	H_7	H_1	H_9	NCH_3
$CDCl_3$	9.80	7.65	7.59	7.18	7.12	6.98	6.85	6.84	3.42
DMSO-d_6	9.72	7.71	7.55	7.23	7.13	7.04	7.00	6.98	3.33
C_6D_6	9.55	7.38	7.34	6.91	6.83	6.67	6.23	6.09	2.49

A preferential conformation of the 3-formyl-10-methyl-phenothiazine structure with respect to the attached formyl group in conjugation with the aromatic nucleus was described.

EXPERIMENTAL

400 MHz Bruker NMR

REFERENCES

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