INFLUENCE OF SOLVENTS ON THE CHEMICAL SHIFTS AND SPIN–SPIN COUPLING CONSTANTS OF PROTONS IN ALKALOIDS

I. HAPLOPHYLLIDINE

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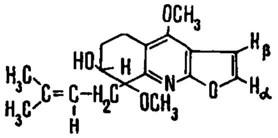
There are many publications on the influence of solvents in NMR spectroscopy [1-3]; nevertheless, it appears of interest to consider the action of solvents on the spectral parameters of such complex substances as alkaloids. Ottinger and Boulvin, studying the influence of solvents, have given an assignment of the $N-CH_3$ signals in caffeine and its derivatives [4]. Information also exists on the relationship between solvents and the parameters of the NMR spectra of alkaloids of the colchicine series [5].

The present paper gives the results of a study of the influence of solvents on the chemical shifts (CSs) and spin–spin coupling constants (SSCCs) of the signals of the protons of the alkaloid haplophyllidine [6].



Its NMR spectrum has been studied previously [7]. All the spectra were obtained on a JNM-4H-100/100 MHz instrument at room temperature (22-23°C) with constant concentrations of the solutions (5%), with the exception of the solution in C_6D_{12} (the majority of natural compounds are insoluble or are sparingly soluble in C_6D_{12}, and because of this the possibility of using it as an inert solvent is excluded).

Tetramethylsilane (TMS) was used as internal standard. The spectral characteristics are given in Table 1. The chemical shifts were determined with an accuracy of ± 0.01 ppm and the SSCCs with an accuracy of ± 0.1-0.2 Hz. Carbon tetrachloride was chosen as the inert solvent since it is less capable (than $CDCl_3$) of associating with a polar functional group of the solute [8]. Positive values of Δ denote a diamagnetic shift relative to CCl_4.

Influence of Aromatic Solvents. It can be seen clearly from the table that the signals of all the protons (with the exception of the OH proton) of haplophyllidine in deuteropyridine appear in a weaker field than in deuterobenzene. The chemical shifts of the gem-dimethyl, the $ArOCH_3$, the H_β, and the H_α protons in benzene are shifted upfield as compared with CCl_4, and the OCH_3 and $\underline{H}-C-OH$ signals downfield. The figures in Table 1 show that pyridine causes a paramagnetic shift of all the signals apart from those of the gem-dimethyl groups, the CSs of which can be considered constant, and the signal of $Ar-OCH_3$, which shifts upfield by 0.14 ppm. These shifts of the signals of the protons in haplophyllidine can apparently be explained by the aromatic interaction of the solvent and the solute [8-12].

Influence of Polar Solvents. In an analysis of the results of the influence of such highly polar solvents as acetone, ethanol, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and acetonitrile the following facts may be noted. The chemical shifts of the gem-dimethyl groups move upfield in ethanol while remaining practically unchanged in the other solvents. A slight diamagnetic shift is observed also for OCH_3 in CD_3CN and DMSO, while $ArOCH_3$ undergoes a slight paramagnetic shift in acetone, ethanol, and DMF. The signals of the olefinic proton and of $H-C-OH$ change insignificantly.

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TABLE 1. Chemical Shifts, Their Relative Differences $\Delta = \delta_{CCl_4} - \delta_{solvent}$, and Spin–Spin Coupling Constants of the Signals of the Protons of Haplophyllidine in Various Solvents

Solvent	Dielectric constant, ε	Chemical shifts of the protons (δ, ppm) and their relative differences (Δ)							Vicinal spin–spin coupling constants (J, Hz)			
		$C\langle^{CH_3}_{CH_3}$	OCH_3	$Ar-OCH_3$	$C\langle^{OH}_{H}$	=CH	H_β	H_α	$J_{CH_\alpha-CH_\beta}$	$J_{=CH-CH_3}$	fragment $^{HO}_{H}\rangle C-C\langle^{H_a}_{H_e}$	
											J_{ee}	J_{ae}
CCl_4	2,24	1,71; 1,76	3,10	4,25	4,08	5,29	6,84	7,49	2,6	6,3	2,5	5,1
C_6D_{12}	2,02	1,67; 1,74 +0,04; +0,02	3,10 0,00	4,15 +0,10	4,04 +0,04	5,39 −0,10	6,79 +0,05	7,36 +0,13	*	—	—	—
CS_2	2,64	1,64; 1,71 +0,07; +0,05	2,98 +0,12	4,20 +0,05	3,91 +0,17	5,20 +0,09	6,84 0,00	7,43 +0,06	2,3	6,5	2,5	4,5
$CDCl_3$	4,55	1,70; 1,75 +0,01; +0,01	3,18 −0,08	4,28 −0,03	4,26 −0,18	5,35 −0,06	6,97 −0,13	7,58 −0,09	2,8	7,0	3,0	6,1
CF_3COOH	8,20	1,37; 1,53 +0,34; +0,23	3,42 −0,32	4,65 −0,40	†	4,71 +0,58	7,43 -0,59	7,87 −0,38	2,4	5,5	†	
C_5D_5N	12,30	1,74; 1,75 −0,03; +0,01	3,34 −0,24	4,11 +0,14	4,57 −0,49	5,73 −0,44	7,04 −0,20	7,78 −0,29	2,6	6,8	2,2	4,4
C_6D_6	2,26	1,65; 1,70 +0,06; +0,06	3,27 −0,17	3,53 +0,72	4,27 −0,19	5,64 −0,35	6,20 +0,64	7,02 +0,47	2,8	7,0	2,1	4,8
$(CD_3)_2CO$	20,70	1,71; 1,76 0,00; 0,00	3,07 +0,03	4,33 −0,08	4,13 −0,05	5,37 −0,08	7,23 −0,39	7,78 −0,29	2,8	6,5	2,3	4,7
CD_3OD	33,60	1,58; 1,68 +0,13; +0,08	3,10 0,00	4,32 −0,07	4,20 −0,12	5,20 +0,09	7,20 −0,36	7,73 −0,24	2,7	7,0	3,5	7,8
$(CD_3)_2NCOD$	36,00	1,72; 1,76 −0,01; 0,00	3,06 +0,04	4,35 −0,10	4,10 −0,02	5,36 −0,07	7,34 −0,50	7,93 −0,44	2,6	6,4	2,3	5,0
CD_3CN	37,40	1,64; 1,72 +0,07; +0,04	3,02 +0,08	4,27 - 0,02	4,12 −0,01	5,25 +0,04	7,13 −0,29	7,68 −0,19	2,5	6,8	2,5	6,2
$(CD_3)_2SO$	49,00	1,68; 1,72 +0,03; +0,04	2,98 +0,12	4,28 −0,03	3,97 +0,11	5,27 +0,02	7,29 −0,45	7,91 −0,42	2,7	6,7	2,3	4,8

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*An accurate determination was impossible because of poor solubility.

†The assignment of δ and J is difficult because of the superposition of other signals.

The H_β and H_α protons of the furan ring are affected most strongly in these solvents; their signals undergo a very pronounced diamagnetic shift (see Table 1).

In order to give a satisfactory explanation of the influence of nonaromatic polar solvents, Onsager put forward the theory of the "reaction field" [13]. The shifts resulting from this effect are usually small and are almost always in the downfield direction [14]. An approximately linear relationship exists between the shift due to the solvent and $(\varepsilon - 1)/(\varepsilon + 1)$ [14].

As can be seen from Table 1, for polar solvents most of the CSs of the protons of haplophyllidine undergo a downfield movement, but there is no satisfactory correlation between Δ and $(\varepsilon - 1)/(\varepsilon + 1)$, which is apparently connected with the complexity of the contribution of the other parameters of the magnetic shielding of the protons. Klinck [15] and Schaefer [16], studying the influence of acetone on the CSs of protons, assumed that one of the positions in the substance was always an acceptor, and a stronger hydrogen bond was formed at this position. The chemical shift of the proton participating in the H bond is displaced considerably in the downfield direction. Starting from this fact and the figures in Table 1,the hypothesis can be put forward that the β proton in haplophyllidine is a stronger acceptor than the α proton.

The greatest changes in the CSs of the signals of the protons in haplophyllidine are found in CF_3COOH. The signals of the gem-dimethyl groups and of the olefinic proton are shifted upfield and those of OCH_3, $ArOCH_3$, and, particularly, H_β and H_α are shifted downfield. In haplophyllidine the paramagnetic shift of OCH_3 ($\Delta = -0.32$) is stronger than in the other solvents in which we performed measurements. Wilson and Williams [17], studying the influence of CF_3COOH on OCH_3 in anisole and p-nitroanisole observed that the signal of the methoxy group undergoes a greater downfield shift than was assumed according to the "reaction field" theory. It is reasonable to assume that the protonation of the OCH_3 is an important factor in determining the downfield shift of the signal of the protons adjacent to the oxygen atom.

Influence of Nonpolar and Weakly Polar Solvents. On comparing the figures in Table 1 for polar and nonpolar solvents, the following facts can be observed: the changes in the CSs caused by nonpolar solvents (C_6D_{12}, CS_2, and $CDCl_3$) are considerably smaller than in polar solvents even for the H_β and H_α protons of haplophyllidine, the signals of which undergo considerable shifts in all the other solvents. Furthermore, in C_6D_{12} and CS_2 there is a tendency to shift upfield (with the exception of $=CH\Delta_{CCl_4}^{C_6D_{12}}=0.1$) and in polar solvents the opposite phenomenon is observed.

For nonpolar and weakly polar solvents, the van der Waals theory of interaction between solvent and solute has been proposed to explain the shifts. Buckingham et al. [1] used the heat of evaporation of the solvent H_b at the boiling point as a measure of the van der Waals interaction. The absence of a correlation between H_b and Δ for haplophyllidine can be explained by the additional influence of the change in the CSs of the magnetic anisotropy of the solvent molecule, the effect of the "reaction field," and the possibility of the formation of associates between the solvent and the solute.

Influence of Solvents on the SSCCs. It was considered that solvents do not appreciably affect SSCCs if they do not lead to conformational or configurational changes. However, a large number of publications on the influence of solvents on J_{gem} are known [18-25]. So far as concerns the action of solvents on the spin–spin coupling constants of the protons of haplophyllidine, it must be observed that although considerable changes in the vicinal SSCCs are observed, these changes are difficult to interpret, since in complex systems they depend on many factors of the interaction of the substance and the medium.

SUMMARY

1. The chemical shifts and spin–spin coupling constants of the protons of the alkaloid haplophyllidine in 12 solvents have been studied.

2. It has been shown that in deuteropyridine the signals are located in a weaker field than in deuterobenzene.

3. The protons of the furan ring undergo the strongest influence of solvents.

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