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SOLVENT SHIFTS IN THE NMR SPECTRA OF α-HALO-β-METHOXY-CARBONYL COMPOUNDS

ASSIGNMENT OF THE α- AND β-PROTON MAGNETIC RESONANCES

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Abstract—The α- and β-proton magnetic resonances of α-chloro- and α-bromo-β-methoxy-β-phenylpropiophenone have been assigned by comparison with the spectra of the corresponding α-deutero-derivatives.

The α-proton solvent shifts induced by acetone and DMSO relative to CCl_4 are also reported. The effect of solvent changes seems to be compatible with the present assignments.

In the course of studies on the chlorination of benzylidenacetophenone in methanol,[1] we suggested that the α-proton resonances of *R,R–S,S-* and *R,S–S,R* - α - chloro - β - methoxy - β - phenylpropiophenone appear at higher field than those for the β-protons. However, we now report NMR results which demand a reverse of the earlier assignments.

When the α-hydrogen is replaced by deuterium, the doublets in the region 4.78–4.85 ppm in the spectra of *R,R–S,S-* (**1a**) and *R,S–S,R* - α - chloro - β - methoxy - β - phenylpropiophenone (**1b**), and *R,R–S,S-* (**2a**) and *R,S–S,R* - α - bromo - β - methoxy - β - phenylpropiophenone (**2b**) in CCl_4 (Table 1) are replaced by singlets, whereas those at lower field disappear.

It was also noticed that the change of solvent from acetone to CCl_4[2] (Table 1) causes the signals due to the α-protons of the compounds **1a** and **1b** to move by 0.30–0.32 ppm to higher field.

In order to test the generality of this observation, the NMR spectra of a number of α - halo - β - methoxy - carbonyl compounds in CCl_4, were compared with those obtained in acetone-d_6 and DMSO-d_6.

When CCl_4 is replaced by acetone-d_6, the α-proton resonances in the spectra of **2a** and **2b** move downfield by 0.42 and 0.39 ppm respectively, whereas the positions of the signals due to the β-protons remain virtually unchanged. A change from CCl_4 to DMSO-d_6 solution causes the resonances arising from the α-protons to move downfield by 0.68 and 0.63 ppm respectively, whereas those for the β-protons undergo only small shifts (Table 1).

The NMR data of Table 1 also show that the signals from the β-protons of **1a** and **1b** in CCl_4, acetone-d_6 or DMSO-d_6 occur at *ca.* 4.80–4.85 ppm, whilst on the other hand, the solvent shifts for the α-protons are similar in size and magnitude to those observed for **2a** and **2b**.

A similar solvent-dependence was observed when the NMR spectra of methyl *R,R–S,S-* (**3a**) and methyl *R,S–S,R* - α - chloro - β - methoxy - β - phenylpropionate (**3b**), and methyl *R,R–S,S-* (**4a**) and methyl *R,S–S,R* - α - bromo - β - methoxy - β - phenylpropionate (**4b**) in CCl_4† were compared with those in acetone-d_6 and in DMSO-d_6. The doublets ascribed to the α-protons undergo downfield shifts on changing from CCl_4 to acetone, but those for the β-protons are much less affected (Table 1).

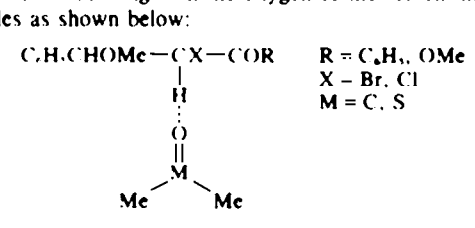
In DMSO solution, the α- and β-protons become equivalent and give rise to a singlet in the region 4.60–4.68 ppm, showing that the effect on the β-protons is much smaller than that on the α-protons. These changes are in reasonably good agreement with the relative magnitude of the shifts observed in the α-proton resonances of ethyl α - chloro - β - hydroxy - β - phenylpropionates when CCl_4 is replaced by DMSO-d_6 as solvent.[3]

The small dependence of the $J\alpha\beta$ on the solvent change indicates that the solvent shifts cannot be explained in terms of conformational changes as an important factor.[4]

It appears then that the position of the α-proton resonance is considerably more sensitive to a change of solvent than that of the β-proton, shifting downfield markedly on going from and "inert" solvent such as CCl_4 to acetone and DMSO.

It is significant that the α-protons are deshielded in H-bond forming solvents. There is good evidence that solvents such as acetone and DMSO show a tendency to associate with solutes containing acidic protons.[5] On the other hand, it is well known that the CO group activates the hydrogens on an adjacent methylene group and that substitution of an electron-attracting halogen for one α-hydrogen increases the acidity of the remaining hydrogen.[6] The observed base-catalysed hydrogen-exchange on carbon α to the CO is a consequence of the acidity of these hydrogens.[7] Furthermore, the isomerisation of CO compounds with an assymmetric α-C atom under basic conditions has also been ascribed to the acidic character of the α-hydrogen.[8]

The pure diastereoisomeric forms of the compounds studied here were all shown to be readily equilibrated to a mixture of the corresponding *R,R–S,S* and *R,S–S,R* isomers with methanol in the presence of a small concentration of sodium methoxide, which provides evidence for the acidity of the hydrogen at α-position. Thus, the observed solvent shifts could be interpreted as resulting from participation of the proton in intermolecular bonding with the oxygen of the solvent molecules as shown below:



†The chemical shifts for the α- and β-protons were assigned by comparison with earlier assignments.[2,3]

Table 1. NMR spectral data of *R,R-S,S-* and *R,S-S,R*-$C_6H_5CHOMeCHXCOR$ (chemical shifts in δ [ppm]; TMS as internal reference; coupling constants in Hz)

R	X	Solvent	Isomer	Chemical shifts				J
				Arom.	H_α*	H_β*	OMe	
C_6H_5	Br	CCl_4	*R,R-S,S*	7.25–8.25	5.04	4.85	3.20	10.0
			R,S-S,R		5.35	4.78	3.32	9.8
		Acetone-d_6	*R,R-S,S*	7.30–8.35	5.46	4.84	3.14	10.0
			R,S-S,R		5.74	4.82	3.25	10.0
		DMSO-d_6	*R,R-S,S*	7.22–8.38	5.72	4.86	3.04	9.8
			R,S-S,R		5.98	4.84	3.18	9.6
	Cl	CCl_4	*R,R-S,S*	7.12–8.14	5.14	4.82	3.15	9.5
			R,S-S,R		5.30	4.80	3.28	7.8
		Acetone-d_6	*R,R-S,S*	7.15–8.30	5.44	4.85	3.12	10.0
			R,S-S,R		5.62	4.85	3.25	7.8
		DMSO-d_6	*R,R-S,S*	7.10–8.35	5.86	4.85	3.00	10.0
			R,S-S,R		6.00	4.85	3.15	8.0
OMe	Br	CCl_4	*R,R-S,S*	7.35	4.16	4.60	3.18	9.8
			R,S-S,R	7.32	4.24	4.62	3.26	7.2
		Acetone-d_6	*R,R-S,S*	7.38	4.38	4.62	3.18	9.8
			R,S-S,R	7.35	4.45	4.64	3.25	7.4
		DMSO-d_6	*R,R-S,S*	7.45	4.60b	4.60b	3.14	0
			R,S-S,R	7.40	4.60b	4.60b	3.20	0
	Cl	CCl_4	*R,R-S,S*	7.36	4.10	4.46	3.25	10.0
			R,S-S,R	7.32	4.20	4.50	3.30	7.8
		Acetone-d_6	*R,R-S,S*	7.42	4.32	4.54	3.18	9.8
			R,S-S,R	7.40	4.35	4.60	3.24	7.8
		DMSO-d_6	*R,R-S,S*	7.45	4.68b	4.68b	3.25	0
			R,S-S,R	7.42	4.68b	4.68b	3.30	0

*Doublets unless otherwise stated; bSinglets.

This solute–solvent association would lead to a deshielding of the α-proton and to the observed downfield shifts.

The larger deshielding effect in DMSO compared with that in acetone is probably due to the stronger solvating ability of the former solvent. This fact might be taken as another indication of the postulated H-bonding solvation.

Inspection of Table 1 also shows that the values of the downfield displacements induced by DMSO in the α-protons of 1, 2, 3 and 4 (a and b respectively) are 0.72 and 0.70, 0.68 and 0.63, 0.58 and 0.48, and 0.44 and 0.36 ppm, respectively. Although these variations in the solvent shifts may be partly due to configurational factors,[9] the relative sensitivities of the α-proton resonances to the solvent change seem† to be in qualitative agreement with the electron-attracting ability of the α-carbon, namely,

$$\text{>C(Cl)(COC}_6\text{H}_5\text{)} > \text{>C(Br)(COC}_6\text{H}_5\text{)} > \text{>C(Cl)(COOMe)} > \text{>C(Br)(COOMe)}$$

which may be taken as a measure of the relative acidities.

Further evidence for the relatively small response of the β-proton resonances to solvent change comes from comparison of the spectral data of α,α-dibromo, α,α-dichloro- and α-bromo-α-chloro-β-methoxy-β-phenylpropiophenone in CCl_4, acetone-d_6 and DMSO-d_6. As can be seen in Table 2 the β-proton signals are only slightly affected.

We conclude therefore that these solvent shifts might be used to differentiate between the α- and β-proton signals of CO compounds. This assumption, however, requires confirmation on a larger number of examples and this work is in progress.

Table 2. NMR spectral data of $C_6H_5CHOMeCXYCOC_6H_5$ (chemical shifts in δ[ppm]; TMS as internal reference)

X	Y	Solvent	Chemical shifts		
			Arom.	H_β	OMe
Br	Br	CCl_4	7.25–8.35	5.08	3.30
		Acetone-d_6	7.25–8.30	5.05	3.28
		DMSO-d_6	7.20–8.32	5.14	3.28
Cl	Cl	CCl_4	7.12–8.20	5.12	3.22
		Acetone-d_6	7.10–8.20	5.10	3.25
		DMSO-d_6	7.05–8.18	5.14	3.25
Br	Cl	CCl_4	7.20–8.28	5.20	3.30a
				5.16	3.38b
		Acetone-d_6	7.15–8.32	5.25	3.28a
				5.15	3.34b
		DMSO-d_6	7.18–8.38	5.26	3.30a
				5.16	3.36b

a*R,R-S,S* isomer; b*R,S-S,R* isomer.

†These differences should be smaller in a less polar solvent such as acetone, and might be overshadowed by a possible counterbalancing influence of the steric factor.

EXPERIMENTAL

The NMR spectra were obtained with a Varian A-60D instrument with a probe temperature of *ca* 35°. Chemical shifts were measured in ppm (δ) from TMS as internal standard. The solutions in the various solvents were 10% wt/vol.

The *R,R-S,S-* and *R,S-S,R-α-halo-β-methoxy-carbonyl compounds* were prepared by halogenation of the appropriate α,β-unsaturated ketone or ester, according to the reported procedure.[1] *α,α-Dichloro-β-methoxy-β-phenylpropiophenone* was prepared by reaction of α-chloro-β-methoxy-β-phenylpropiophenone (0.001 mole) with t-butyl hypochlorite (0.0025 mole) in MeOH (20 ml) containing 0.002 mole of NaOMe at room tem. After 10 min, the mixture was poured into water and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. *α,α - Dibromo - β - methoxy - β - phenylpropiophenone* was prepared from α - bromo - β - methoxy - β - phenylpropiophenone (0.001 mole) by treatment with bromine (0.005 mole) in MeOH containing NaOMe (25 ml; 0.0025 mole). After 15 min at room temp. the mixture was poured into water and worked-up as described above. Similar treatment of α - chloro - β - methoxy - β - phenylpropiophenone gave a mixture of R,R-S,S- and R,S-S,R - *bromo - α - chloro - β - methoxy - β - phenylpropiophenone*. The mixture was then dissolved in light petroleum (b.p. 40–60°) and chromatographed on silica gel. One of the isomers was eluted with a mixture of benzene and light petroleum (1:1). The other isomer was eluted with benzene and chloroform (1:1). The configurational assignment of these isomers was based on comparison of the Hβ and MeO chemical shifts with those for the α - halo - β - methoxy - β - phenylpropiophenones.

Equilibration reactions To a soln of 0.0025 mole of the appropriate *R,R-S,S* - α - halo - β - methoxy - β - phenylpropiophenone in MeOH (50 ml) was added a soln of 0.0005 mole of NaOMe in 50 ml MeOH. The mixture was allowed to stand for 30 min at room temp., and then poured into water and extracted with $CHCl_3$. The extract was washed with water and evaporated under reduced pressure. The NMR spectrum of the residue was measured directly.

The equilibrations of methyl *R,R-S,S* - α - halo - β - methoxy - β - phenyl - propionates were carried out analogously except that 0.002 mole of NaOMe was used. α - Deutero - α - halo - β - methoxy - β - phenylpropiophenones (*R,R-S,S* and *R,S-S,R* respectively) were obtained in a similar manner to that described for the equilibration reactions except that MeOD was used in place of MeOH. The diastereoisomers were separated in the usual manner, and the configurations assigned by comparison of the chemical shifts of the β-hydrogens and the OMe groups with those for the α-hydrogen compounds.

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