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SOLVENT SHIFTS INDUCED BY DIMETHYLSULPHOXIDE IN α-PROTON MAGNETIC RESONANCES OF CARBONYL COMPOUNDS

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Abstract—The chemical shifts of α- and β-proton resonances of a number of carbonyl compounds in carbon tetrachloride and dimethylsulphoxide have been determined. The magnitude of the effect of the solvent change on the α-proton resonances seems to vary directly with its lability.

Previously[1] we reported the solvent shifts induced for the α-proton resonances in some α-chloro and α-bromo-β-methoxy esters and ketones by acetone and DMSO relative to carbon tetrachloride. The generality of this observation has now been tested for a number of other carbonyl compounds.

The observed α-proton chemical shifts were interpreted in terms of intermolecular H-bond with the oxygen of the solvent as hydrogen acceptor $[\rangle C\text{—}H\text{—}O{=}SMe_2]$. In order to be able to assess the validity of this assumption and to gain more information regarding the nature of this solvent-substrate association, we were interested in examining to what extent differences in the solvent shifts of the α-hydrogens can be related to the relative ability of the C_α–H group to function as a proton donor.

Values of ionisation constants for the C_α–H group in the compounds studied here cannot of course be measured. However, the relative acidities of each pair of the α-halo-β-methoxy carbonyl diastereomers can be evaluated. The base-induced equilibration of the *R, R-S, S* esters and ketones[1] to mixtures with their corresponding *R, S-S, R* forms in MeOD has been found to occur with α-deuterodeprotonation. The results indicated that the rates of α-hydrogen exchange and equilibration were equal. This may be interpreted as involving proton abstraction from the α-C atom followed by protonation of the resulting carbanion.[2] It is a thermodynamic principle that the form which predominates will always be the least acidic of all the possible forms giving rise to a common ion. Since the equilibration seems to take place through a common carbonionic intermediate, the ratio of the isomers gives the relative acidities, according to the Scheme:

$$R, R\text{-}S, S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{ANION} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R, S\text{-}S, R$$

$$K_{eq} = \frac{k_1 k_{-2}}{k_{-1} k_2} = \frac{K_a(R, R\text{-}S, S)}{K_a(R, S\text{-}S, R)} = \frac{[R, S\text{-}S, R]}{[R, R\text{-}S, S]}$$

Contrary to the expectation that the more acidic C_α–H were associated with the larger solvent shifts, inspection in Table 1 of the figures for equilibrium constants and Δ values (δ_{DMSO}–δ_{CCl_4}) reveals that a reversal of what would be assumed was obtained.

Another approach to the problem involved estimation of the relative rates of abstraction of the α-H atom and comparison of these with the relative magnitudes of the solvent shifts for each pair of diastereomers.

Since the α-halo-β-methoxy esters and ketones stu-

Table 1. α-Proton solvent shifts (ppm), equilibrium constants and relative kinetic acidities for various α-halo-β-methoxy carbonyl compounds (a) and their diastereomers (b), $C_6H_5CHOMeCHXCOR$

X	R	Isomer[x]	$\delta_{DMSO}-\delta_{CCl_4}$	K_{eq} = b/a	k_a/k_b
Cl	OMe	a	0.58	0.59	1.39
		b	0.47		
	C_6H_5	a	0.72	0.82	1.16
		b	0.70		
Br	OMe	a	0.44	0.61	1.43
		b	0.36		
	C_6H_5	a	0.68	0.74	1.19
		b	0.61		

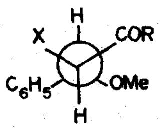
[x] a = R,R–S,S; b = R,S–S,R

died are very weak acids, their ionisation rates must be much smaller than the rates of their formation from the anion ($k_{-1} \gg k_1$ and $k_2 \gg k_{-2}$). As a reasonably good measure of the relative rates of ionisation, the ratio of the rates of α-hydrogen exchange could be taken.[3]

The relative rates of methoxide-promoted α-deuterodeprotonation in MeOD–DMSO for each of the diastereomer-pairs are given in Table 1. The susceptibilities of the position of the α-proton resonance signals to the solvent change showed to agree qualitatively with the corresponding ease of proton transfer.

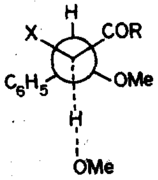
At first sight this seems rather surprising as one naively expects agreement between kinetic and thermodynamic acidities of related compounds. However, it has been recognised that the structural features that serve to stabilise a carbanion wouldn't be necessarily expected to stabilise the activated complex leading to it.[4]

The ionisation almost certainly proceeds through the H-bonded complex $[{>}C{-}H{-}OMe]^-$. Inspection of molecular models of the α-halo-β-methoxy carbonyl compounds together with the coupling constant values ($J\alpha\beta$)[1] suggests that the conformations with antiperiplanar protons (I and II) would predominate in all cases both for the *R*, *R*–*S*, *S* and *R*, *S*–*S*, *R* isomers.[5] From considerations of non-bonded interactions it can be assumed that the transition state from the *R*, *S*–*S*, *R* isomers (**2a**) should be more sterically restricted than the transition state from the corresponding *R*, *R*–*S*, *S* forms (**1a**).

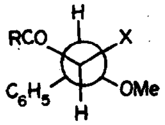


R,R—S,S

1

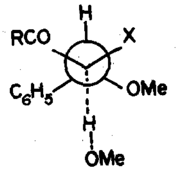


1a



R,S—S,R

2



2a

Since the differences in stability between each pair of diastereomers are not large (Table 1), it is not unreasonable to suggest that the above considerations could explain the fact that $k_{-2} < k_1$.

When the basic species is absent, the role of the base may be played by the molecule of a strong H-bond acceptor such as DMSO. However, neither isomerisation nor deuterodeprotonation were observed when the pure diastereomers were set aside in DMSO alone or containing MeOD at room temperature for several days.

There would seem to be no strong reason to believe that the transition state for H-transfer would resemble the H-bonded complex proposed for the solvent-substrate association. However, it is apparent that the factors determining the degree of the solvent-solute interaction are closely allied to those governing the kinetic acidity of the α-proton.

The solvent shifts ($\Delta^{CCl_4}_{DMSO}$) for some α-halo-β-acetoxy esters and ketones are similar in size and sign to those observed for the parent β-methoxy compounds (Table 2).

When the α-halo-β-acetoxy carbonyl compounds were treated with methanolic dimethylsulphoxide containing different concentrations of sodium methoxide only dehydroacetoxylation took place without preequilibrium carbanion formation, since absence of proton exchange and no isomerisation were observed.

The methoxide-promoted β-elimination reaction in methanol–DMSO was shown to follow first-order dependence on [NaOMe] and general base catalysis.[6] These observations are consistent[7] both with a process in which the breaking of the C_α–H and $C\beta$–OAc bonds is concerted (E_2), and with rate-determining carbanion formation followed by a rapid loss of acetate $(E_{1c}B)_I$.

It is rather difficult to distinguish between the concerted and the irreversible carbanion mechanisms.[7] However, the lack of dependence of rate on the nature of the 4-substituents in the benzylic ring[6] might be taken as indicative of reaction involving solely C_α–H breaking in the slow step. Comparable systems have proved that when methoxide is replaced by a better leaving group such as OAc[8] the irreversible carbanion mechanism of elimination obtains.

If the $(E_1cB)_I$ is operative in the present case, then it is concluded that the solvent shift induced in DMSO is greater for the isomer with larger C_α–H lability (Table 2).

Although the general trend of the experimental data suggests a dependence between the effect of DMSO on the α-hydrogen resonances and their kinetic acidities a quantitative correlation could not be established. The explanation of this is to be found, we suggest, in different conformational changes in the isomers arising from the size of the DMSO molecule. These changes, though small as can be judged from the effect of the solvent change on the coupling constant values[1] (Table 2), could be partly responsible for differences in the observed shifts.

The dependence on the solvent change of a number of $\alpha\beta$-dihalo carbonyl compounds were also examined (Table 3). The results indicate that the resonances of the α-hydrogens behave similarly to those of the β-methoxy and β-acetoxy esters and ketones, and are in agreement with the proposed solvent-solute interaction. Attempts to estimate the ease of α-hydrogen transfer of these compounds in basic conditions led to dehydrohalogenation in all cases. If the relative rates of these eliminations are a measure of the relative rates of hydrogen abstractions, then Table 3 indicates that the magnitude of the shifts varies directly with the lability of the proton for each pair of diastereomers. However, further studies are required before a decision can be made about the mechanism of these reactions.

Additional evidence for shifts associated with C_α–H adjacent to CO in DMSO relative to carbon tetrachloride is presented in Table 4.

On the basis of the present results it seems that the susceptibility of the α-proton resonances to change from an "inert" solvent to a H-bond forming solvent such as DMSO depends on its facility for ionisation, and that it can be used to differenciate between α- and β-proton resonances in carbonyl compounds.

Table 2. NMR spectral data (δ in ppm, J in Hz) and relative dehydroacetoxylation rates in diastereomeric $C_6H_5CHOAcCHXCOR$ (a and b)

X	R	Isomer	Solvent	H^{x}_{α}	H^{x}_{β}	$J_{\alpha\beta}$	k_a/k_b
Cl	OMe	a	CCl_4	4.60	6.25	8.0	1.82
			DMSO	4.95	6.13	8.2	
		b	CCl_4	4.62	6.14	8.3	
			DMSO	4.88	6.10	9.0	
	C_6H_5	a	CCl_4	5.52	6.40	8.2	2.67
			DMSO	6.36	6.44	8.5	
		b	CCl_4	5.42	6.32	9.5	
			DMSO	6.18	6.38	9.0	
Br	OMe	a	CCl_4	4.50	6.10	9.0	1.95
			DMSO	5.06	6.12	9.2	
		b	CCl_4	4.62	6.08	9.8	
			DMSO	5.08	6.05	9.8	
	C_6H_5	a	CCl_4	5.52	6.45	10.6	2.20
			DMSO	6.45	6.42	10.2	
		b	CCl_4	5.38	6.34	10.8	
			DMSO	6.18	6.35	10.5	

[x] Confirmation of these assignments was provided by comparison with resonances in $C_6H_5CDOAcCHXCOR$.

Table 3. NMR spectral data (δ in ppm, J in Hz) and relative dehydrohalogenation rates for diastereomeric $C_6H_5CHXCHXCOR$ (a and b)

X	R	Isomer	Solvent	H^{x}_{α}	H^{x}_{β}	k_a/k_b
Cl	OMe	a	CCl_4	4.70	5.32	7.45
			DMSO	5.72	5.45	
		b	CCl_4	4.68	5.20	
			DMSO	5.52	5.35	
	C_6H_5	a	CCl_4	5.42	5.42	9.28
			DMSO	6.35	5.51	
		b	CCl_4	5.42	5.42	
			DMSO	6.22	5.50	
Br	OMe	a	CCl_4	4.62	5.30	5.30
			DMSO	5.54	5.36	
		b	CCl_4	4.77	5.25	
			DMSO	5.56	5.30	
	C_6H_5	a	CCl_4	5.72	5.70	8.25
			DMSO	6.74	5.82	
		b	CCl_4	5.78	5.65	
			DMSO	6.60	5.78	

[x] Confirmation of these assignments was provided by comparison with proton resonances in $C_6H_5CDXCHXCOR$.

Table 4. α-Proton solvent shifts (ppm) for some carbonyl compounds

Compound	$\delta_{DMSO} - \delta_{CCl_4}$
$C_6H_5COCH_3$	0.08
$C_6H_5COCH_2Br$	0.54
$C_6H_5CH_2COOMe$	0.19
$C_6H_5CH_2COC_6H_5$	0.24
$C_6H_5CHClCOC_6H_5$	1.07
$C_6H_5\underset{Me}{C}BrCHBrCOOMe$	0.50
$C_6H_5\underset{OMe}{C}MeCHBrCOOMe$	0.28
$C_6H_5CHCl\underset{C_6H_5}{C}HCOOMe$	0.74

EXPERIMENTAL

The NMR spectra were measured at 38° with a Varian A-60D instrument on 10% wt/vol solutions. All chemical shifts are recorded as δ values in ppm downfield from TMS as internal reference.

Mixtures of the *R, R–S, S* and *R, S–S, R* α-halo-β-methoxy esters and ketones were prepared and the pure diastereomers separated as reported previously.[9]

The α-chloro-β-acetoxy compounds were prepared by action of t-butyl hypochlorite on the appropriate unsaturated ester or ketone in acetic acid according to the reported procedure.[10] The α-bromo-β-acetoxy compounds were obtained similarly except that N-bromosuccinimide was used as the halogenating agent.[11]

The β-deutero compounds were prepared from the corresponding β-deutero olefin. The latter was obtained by condensation of C_6H_5CDO with malonic acid or acetophenone.

Methyl αβ-dibromo and methyl α-bromo – β-methoxy – β-methyl – β-phenylpropionate were prepared by bromination of methyl β-methyl cinnamate with Br_2 in chloroform and with N-bromosuccinimide in MeOH respectively.

Equilibration reactions. The equilibration methods were as described previously.[1] Analysis of the equilibrated mixtures were effected by NMR spectroscopy from the areas under the β-methoxy resonance peaks.

α-Deuterodeprotonation reactions. The relative rates of deuterodeprotonation were measured in a thermostatically controlled bath at 30 ± 0.2°. Samples of mixtures containing a total of 0.05 mmol of the diastereoisomers were added to solns of NaOMe in DOMe–DMSO (1:3) (10 ml; 0.0025 M). After 1 min the solns were neutralised with DCl. The ratio of the rates was established by integration of the Hβ signals in the NMR spectrum and estimation of the proportions of unexchanged material.

Dehydroacetoxylation reactions. Samples of the α-halo-β-acetoxy compounds (0.02 M) and NaOMe (0.01 M) in MeOH–DMSO (3:1) were mixed in a flask in the thermostat (30 ± 0.2°). Aliquots were withdrawn at various time intervals, quenched in cold water and extracted with $CHCl_3$. The solvent was evaporated and the residue analysed by NMR. Proportions of eliminated material were estimated from integrals of the acetoxy-protons signals.

Dehydrohalogenation reactions. Runs were started by mixing the corresponding αβ-dihalo carbonyl compound (0.001 mol) with a soln of NaOMe in MeOH–DMSO (3:1) (50 ml; 0.02 M). Portions were withdrawn at appropriate intervals, quenched in cold water and extracted with $CHCl_3$. The solvent was removed and the sample analyzed by NMR. Rate constants were calculated by standard methods for second-order reactions.

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