Solvent Effects on the Chemical Shifts of Halogenated Derivatives of Diphenyl Sulphone, Dibenzothiophene and Dibenzothiophene 5,5-Dioxide

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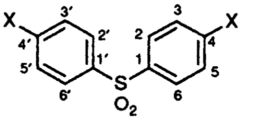
The ^1H NMR spectra of the title compounds were recorded in [$^2H_6$]DMSO and $CDCl_3$ solvents and analysed using the LAOCOON-3 program. A different degree of shielding of the two protons *ortho* to the halogen atoms was observed in the tricyclic compounds. The sign and the magnitude of this differential shielding depends on both the halogen substituent and the solvent. Models for the solute–solvent interactions are suggested, and it is proposed that both mesomeric and steric effects contribute to the observed NMR results.

The fundamental role of intermolecular interactions in the biological activity of chemical compounds is well known. Therefore, the experimental detection of this type of interaction would be very useful for predicting molecular behaviour in different environments.

The solvent effect on the chemical shifts of the ^1H NMR resonances would provide a tool with which to detect such intermolecular interactions. From the early work by Bothner-By,[1] the solvent effect on chemical shifts has been widely investigated and many reviews have appeared such as those of Laszlo,[2] Foreman[3] and Rummens.[4] Several models of solute-solvent interactions have been proposed to interpret the effect of the solvent on the resonance frequency of the protons, *e.g.* the 1:1 collision complexes proposed by Ledaal,[5] and the time-averaged cluster or cage of solvent molecules surrounding one solute molecule reported by Laszlo,[6] Homer[7] and Rummens,[8] who were mainly concerned with aromatic solvents.

This paper gives an interpretation of solute–solvent intermolecular interactions based on NMR measurements for a series of halogenated derivatives of diphenyl sulphone, **1**, dibenzothiophene 5,5-dioxide, **2**, and dibenzothiophene, **3**. The experiments were carried out in [$^2H_6$]DMSO and $CDCl_3$ as solvents.



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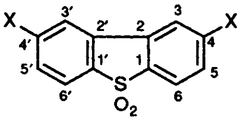

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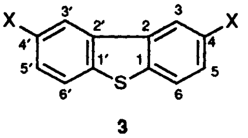

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a X = H
b X = F
c X = Cl
d X = Br

Results and Discussion

^1H and ^{13}C NMR spectra were recorded for series **1** and **3**, however only ^1H NMR spectra were recorded for series **2** because of the low solubility of the halogenated compounds **2b–d**.†

Tables 1 and 2 list the chemical shifts and coupling constants, respectively, as calculated with the LAOCOON-3 program. ^1H NMR spectra of compounds **1a**,[9a] **1c**,[9a] **2a**[10] and **3a**[10–14] have previously been studied, in particular the spectrum of **3a**. ^1H NMR and ^{13}C NMR spectra of **1a–d** have recently been published.[9b]

As expected, the 3-H, 3'-H, 5-H and 5'-H signals were shifted to high fields by the fluorine atoms, while both *ortho* positions were deshielded by bromine atoms. The effects of chlorine on the chemical shifts varied in each case. Thus, in [$^2H_6$]DMSO there was little change in the chemical shifts of *ortho* protons from **1a**–**1c**, whereas in compounds **2c** and **3c** a larger deshielding was observed for protons in position 3 than in position 5. When measurements were carried out in deuteriochloroform both *ortho* signals remained almost unchanged in compounds **1c**, **2c** and **3c** relative to the non-halogenated compounds. The most interesting observation was the small but nevertheless measurable extent to which the two *ortho* protons in compounds **2b–d** and **3b–d** tend to be shielded to different degrees by the halogen atom. Table 3 summarizes the differences between the resonance frequencies of 3-H and 5-H in the halogenated compounds relative to those of the same protons in the parent 4-H molecules. In [$^2H_6$]DMSO solutions, 3-H was less shielded than 5-H by fluorine, particularly in compound **2b**. In the case of the 4-Cl and 4-Br compounds, 3-H was more deshielded than 5-H. When the spectra were recorded in $CDCl_3$ solutions the 3-H signal was more shielded by fluorine than that of 5-H; while the effects of chlorine and bromine on both positions were very similar.

A comparable difference in the chemical shifts of the two protons *ortho* to the substituents in a series of benzothiophene and benzothiophene 1,1-dioxide in $CDCl_3$ solutions have been previously reported by Chapman *et al.*[15] They proposed that the difference arises from the mesomeric effect, +M, which produces an unequal change in the electron density at the two

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† The numbering of compounds **2** and **3** was chosen to allow comparison with that of compounds **1** and therefore does not follow IUPAC rules.

Table 1. Proton chemical shifts of compounds **1**–**3** (ppm).

Compound	[$^2H_6$]DMSO					RMS errors/Hz	$CDCl_3$					RMS errors/Hz
	2-H	3-H	4-H	5-H	6-H		2-H	3-H	4-H	5-H	6-H	
1a	7.966	7.589	7.641	7.589	7.966	0.151	7.972	7.464	7.517	7.464	7.972	0.139
1b	8.095	7.487	—	7.487	8.095	0.087	8.019	7.237	—	7.237	8.019	0.093
1c	7.964	7.689	—	7.689	7.964	0.041	7.961	7.487	—	7.487	7.961	0.035
1d	7.848 ^{a}	7.848 ^{a}	—	7.848 ^{a}	7.848 ^{a}	—	7.825	7.665	—	7.665	7.825	0.013
2a	—	8.181	7.789	7.647	7.962	0.130	—	7.825	7.493	7.597	7.788	0.219
2b	—	8.174	—	7.522	8.087	0.053	—	7.447	—	7.300	7.970	0.074
2c	—	8.462	—	7.747	8.044	0.040	—	7.806	—	7.534	7.811	0.027
2d	—	8.603	—	7.843	7.987	0.032	—	7.951	—	7.733	7.733	0.043
3a	—	8.226	7.383	7.525	7.904	0.082	—	8.043	7.347	7.354	7.754	0.167
3b	—	8.165	—	7.415	8.061	0.055	—	7.780	—	7.222	7.737	0.030
3c	—	8.600	—	7.580	8.083	0.035	—	8.110	—	7.422	7.767	0.018
3d	—	8.747	—	7.690	8.033	0.041	—	8.289	—	7.593	7.763	0.036

^{a} Central position of a non-resolved symmetric multiplet.

Table 2. Coupling constants^a/Hz.

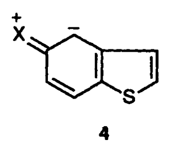
Compound	$J_{2,3}$	$J_{2,4}$	$J_{2,5}$	$J_{2,6}$	$J_{3,4}$	$J_{3,5}$	$J_{3,6}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	Solvent
1a	8.014	1.214	0.405	2.210	7.696	1.790	0.405	7.696	1.214	8.013	[$^2H_6$]DMSO
1b	8.645	5.003 ^{b}	0.045	2.545	8.642 ^{b}	2.603	0.045	8.642 ^{b}	5.003 ^{b}	8.645	[$^2H_6$]DMSO
1c	8.830	—	0.183	2.330	—	2.330	0.183	—	—	8.830	[$^2H_6$]DMSO
1d	—	—	—	—	—	—	—	—	—	—	[$^2H_6$]DMSO
2a	—	—	—	—	7.058	1.297	0.007	7.184	1.411	7.181	[$^2H_6$]DMSO
2b	—	—	—	—	8.812 ^{b}	2.122	0.028	8.812 ^{b}	5.272 ^{b}	9.351	[$^2H_6$]DMSO
2c	—	—	—	—	–	1.895	0.306	—	—	8.170	[$^2H_6$]DMSO
2d	—	—	—	—	–	1.530	0.528	—	—	8.402	[$^2H_6$]DMSO
3a	—	—	—	—	7.865	2.910	0.033	7.064	2.964	7.164	[$^2H_6$]DMSO
3b	—	—	—	—	8.814 ^{b}	2.710	0.024	8.814 ^{b}	5.046 ^{b}	9.137	[$^2H_6$]DMSO
3c	—	—	—	—	—	1.567	0.358	—	—	8.809	[$^2H_6$]DMSO
3d	—	—	—	—	—	1.946	0.440	—	—	8.522	[$^2H_6$]DMSO
1a	8.775	1.537	0.616	1.853	8.819	2.358	0.616	8.819	1.537	8.775	$CDCl_3$
1b	8.943	5.457 ^{b}	0.017	2.879	8.988 ^{b}	2.907	0.019	8.988 ^{b}	5.457 ^{b}	8.943	$CDCl_3$
1c	8.018	—	0.213	3.025	—	3.025	0.213	—	—	8.018	$CDCl_3$
1d	8.827	—	0.090	1.955	—	1.955	0.090	—	—	8.827	$CDCl_3$
2a	—	—	—	—	7.621	1.085	0.051	7.703	1.128	7.803	$CDCl_3$
2b	—	—	—	—	8.949 ^{b}	2.617	0.114	8.949 ^{b}	5.437 ^{b}	8.783	$CDCl_3$
2c	—	—	—	—	—	1.905	0.319	—	—	8.207	$CDCl_3$
2d	—	—	—	—	—	1.397	0.000	—	—	—	$CDCl_3$
3a	—	—	—	—	8.196	1.802	0.078	7.763	1.763	7.883	$CDCl_3$
3b	—	—	—	—	8.927 ^{b}	2.989	0.054	8.927 ^{b}	5.132 ^{b}	9.305	$CDCl_3$
3c	—	—	—	—	—	2.761	0.297	—	—	8.975	$CDCl_3$
3d	—	—	—	—	—	3.054	0.062	—	—	9.162	$CDCl_3$

^{a} $J_{H.H}$. ^{b} $J_{F.H}$.

Table 3. Differential chemical shifts (Δ)^a of protons *ortho* to halogen atoms in compounds **2** and **3**.

Compound	4-X	Δ([$^2H_6$]DMSO)		Δ($CDCl_3$)	
		3-H	5-H	3-H	5-H
2b	F	−0.01	−0.12	−0.37	−0.29
2c	Cl	+0.28 ^{b}	+0.10	−0.02	−0.06
2d	Br	+0.42	+0.19	+0.12	+0.13
3b	F	−0.06	−0.11	−0.26	−0.13
3c	Cl	+0.37	+0.05	+0.06	+0.06
3d	Br	+0.52	+0.17	+0.24	+0.24

^{a} $\Delta_{(H-n)} = \delta n_{(4-X)} - \delta n_{(4-H)}$ (ppm). ^{b} Positive sign corresponds to downfield shifts and negative sign to upfield shifts.



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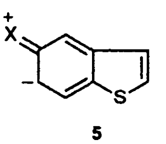

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ortho positions, since the canonical structure **4** contributes more to the ground state than the canonical structure **5**.

The chemical shift differences observed upon changing the solvent found in the present work, could arise through a variety of effects. Initially, the transmission of the electronic effects[15] introduced by an isolated halogen atom are likely to be influenced to some extent by association with the solvent. This arises due to variations in bonding with solvent molecules in their specific orientations. An additional explanation for the observed behaviour could be a steric effect due to conformational variations induced or stabilized by specific solute–solvent interactions.

It is well known that dibenzofuran and dibenzothiophene have a slight boat conformation in the solid state.[16] If their structures were planar, the hydrogen atoms 3-H and 3′-H would

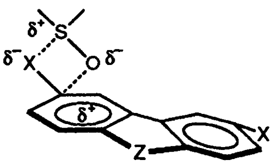

Fig. 1. Solute–solvent perpendicular interaction.

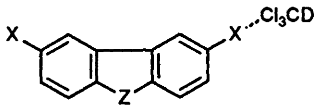

Fig. 2. Head on solute–solvent interaction.

be nearer and the Van der Waals repulsion would be higher. For this reason, the non-planar conformation is preferred and the nuclei of 3-H and 3′-H are more shielded than in a planar molecule. If they were at a shorter distance than the sum of the Van der Waals radii the electronic repulsion would produce deshielding of the 3-H and 3′-H nuclei. Therefore, factors that favour the molecular planarity would relatively deshield protons 3-H and 3′-H while factors that hinder the molecular planarity or stabilize the boat conformer would produce a relatively larger shielding of those protons. This explanation is applicable either in the solid state or in solution because they are relative effects.

The introduction of halogen atoms in positions 4 and 4′ is the only structural change introduced in compounds **2b–d** and **3b–d** by comparison with **2a** and **3a**, respectively. Therefore, the different behaviour observed with the change of solvent must be caused by carbon–halogen bond interactions with solvent molecules.

After analysis of a large amount of data from the Cambridge Crystallographic Data Centre, Partharasathy and co-workers[17] proposed two preferred directions for intermolecular contacts in compounds with carbon–halogen bonds. These directions depend on the electrophilic or nucleophilic nature of the other particles under consideration. Electrophiles would approach the carbon–halogen bond with angles of *ca.* 90°, whereas nucleophiles would make 'head on' contacts with angles of *ca.* 180°. Halogen–halogen interactions may occur in two ways: the first implies that one halogen atom acts as a nucleophile and the other as an electrophile. The second takes place without participation of such pairing. The calculations were carried out by analysing crystal structures, the foregoing considerations also accounting for solute–solvent interactions.

On the other hand, Politzer and co-workers[18] calculated the electrostatic potentials created in their surrounding space by molecules of dibenzofuran, dibenzodioxin and halogenated dibenzodioxins. The results reported demonstrate the presence of a high negative potential above the unsubstituted outer rings due to the π electrons. This negative region is eliminated by partial substitution of hydrogen by halogen atoms, and a region of positive electrostatic potential is located above the outer rings. While a strong negative potential appeared in the lateral region above the chlorine atoms, the magnitude of this negative region is reduced by more than 50% in the vicinity of fluorine atoms.

The calculated values of the electrostatic potentials facilitate a qualitative prediction of possible interactions of this type of molecules with their environment. These predictive considerations can be extended to our compounds due to their structural similarity with those studied by Politzer.

Based on the model of the oriented intermolecular contacts and on the model of the surrounding molecular electrostatic potentials mentioned above, we propose the following method of solute–solvent interactions which could account for the observed dependence of the chemical shifts on both the halogen substitution and the nature of the solvent.

Table 4. ^{13}C Chemical shifts (ppm) in CDCl$_3$.

Compound	C-1	C-2	C-3	C-4	C-5	C-6
1a	141.3	127.3	129.1	133.1	129.1	127.3
1b	137.4	130.9	116.5	165.3	116.5	130.9
1c	140.4	129.0	129.6	139.6	129.6	129.0
1d	141.0	130.2	133.6	129.4	133.6	130.2
3a[a]	139.1	135.2	121.2	124.0	126.3	122.4
3b	135.6	136.0	107.8	166.6	115.4	123.8
3c	138.1	135.7	121.5	130.8	127.4	123.7
3d	138.4	136.0	124.5	118.4	130.1	124.0

[a] Data from ref. 23.

Very polar [^{2}H$_6$]DMSO molecules could strongly associate with the halogenated substrates **2b–d** and **3b–d** in a close contact normal to the carbon–halogen bond, as shown in Fig. 1.

The nucleophilic oxygen atom from the solvent would be attracted by the carbon atom whose electrophilic character is increased by the next positive region on the aromatic ring. In turn, the negative field around the halogen centres would attract the sulphur atom in the solvent.

This layered disposition would favour a more planar conformation in the solute molecules. Consequently, 3-H and 3-H′ would be close enough to produce electronic repulsion and as a result the nuclei will be deshielded. As the electrostatic potential around the fluorine atom is lower than that of the chlorine or bromine, the polar interaction of **2b** and **3b** with the solvent must also be lower and the molecules would adopt a less planar conformation than that of **2c**, **d** and **3c**, **d**. This leads to a relatively less deshielding of protons in positions 3 and 3′ of compounds **2b** and **3b**.

The behaviour of CDCl$_3$ could be considered as opposite to that of [^{2}H$_6$]DMSO since 3-H and 3′-H undergo a degree of shielding which is different from that of 5-H and 5′-H only in the fluorinated derivatives. This effect is negligible in the other halogenated compounds. It becomes evident that the preferred conformation of the halogenated solutes in CDCl$_3$ would be less planar than that of the non-halogenated solutes. This suggests that solvent interactions with bromo- and chloro-derivatives take place in a 'head on' fashion, as represented in Fig. 2.

Table 4 presents the ^{13}C NMR chemical shifts of the series of compounds **1** and **3** in CDCl$_3$. The ^{13}C NMR of the chloro- and bromo-derivatives **3c** and **3d** show little differences in the shielding of the carbon atoms *ortho* to the halogens. These results agree with their ^{1}H NMR spectra, and are expected from the solvent interactions that occur on the lateral region of the rings without significantly affecting the molecular planarity.

Conclusions

Previously, the mesomeric effect, +M, has been proposed[15] as being responsible for the different chemical shifts occurring in both *ortho* positions to the halogen atoms in compounds structurally related to the substrates described in this paper. This effect would occur by partial double-bond fixation, which would be more efficient with fluorine atoms than with the other halogens. Although the change of solvent would be expected to influence the transmission of the mesomeric effect to some extent, there are, nevertheless, some important results which still remain to be explained. First, the opposite sign of the differential shifts ($\delta_3 - \delta_5$) observed in the spectra of the fluorine compounds **2b** and **3b** when the solvent was changed from [^{2}H$_6$]DMSO to CDCl$_3$. Secondly, the reason why ($\delta_3 - \delta_5$) increases in the order F < Cl < Br in [^{2}H$_6$]DMSO solutions whereas there was almost no difference in the spectra recorded in $CDCl_3$ solutions for chlorinated and brominated compounds.

Therefore, a solvation model in which at least the inner shell of solvent molecules would have a preferred orientation with respect to the carbon–halogen bonds, is proposed. In this way, the planarity of solute molecules is modified by the steric hindrance produced by the complexed solvent and the shielding on the 3 and 3′ positions is changed. This model of solute–solvent interactions together with the differential mesomeric effect would account for the results reported in this paper.

Experimental

Diphenyl sulphone, **1a** (Fluka), and 4,4′-difluorodiphenyl sulphone, **1b** (Pierce), were commercially available.

The remaining compounds were prepared following reported procedures; **1c**;[19] **1d**;[20] **2a**;[21] **2b** and **3b**;[21b] **2c** and **3c**;[19a] **2a**;[19a,21a] **3a** [21a] and **3d**.[22]

The ^1H NMR spectra were recorded on a Bruker 80 FT spectrometer at 80.13 MHz and on a Varian EM 390 spectrometer at 90 MHz. The ^{13}C NMR spectra were performed on a XL 100A FT 16K spectrometer operating at 25.2 MHz. All spectra are referred to internal Me_4Si. Sample concentrations were 0.5 mol dm^{-3} except for compounds **3c** and **3d** in $CDCl_3$ as solvent where the concentrations were lower due to their poor solubility.

The ^1H NMR spectra were simulated using the LAOCN3 version of the LAOCOON-3 Program[24] on an IBM 4330 computer.

Acknowledgements

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