A Study of Steric and Electronic Effects in Some Methane- and Dimethane-sulphonanilides by ^{13}C NMR Spectroscopy

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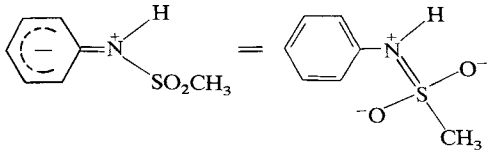
The steric and electronic interactions in several methanesulphonanilides and dimethane-sulphonanilides have been examined on the basis of their ^{13}C NMR chemical shifts. In aromatic amines there is evidence of nitrogen electron pair donation into the aromatic ring. However, the substitution of a methanesulphonyl group on nitrogen, as in *N*-phenylmethanesulphonamide, causes a decrease in this resonance interaction. The chemical shifts of *ortho*- and *para*-carbons therefore move downfield in comparison with the corresponding amines. Substitution of the aromatic ring at the *para* position by electron-withdrawing and electron-donating groups affects the resonance process. The substitution of methyl groups either at nitrogen or at the *ortho* positions causes severe steric inhibition of resonance, which is clearly reflected in the chemical shifts of these compounds. The chemical shifts in several dimethane-sulphonanilides have also been examined and compared with the shifts in the corresponding methanesulphonanilides. The observed differences are explained in terms of steric, mesomeric and inductive interactions in these molecules. The preferred conformations of these compounds in solution are also postulated on the basis of their chemical shifts.

INTRODUCTION

Compounds based on a sulphonanilide nucleus (Ar-$NHSO_2R$) are important from a biological point of view, and have been shown to possess antileukaemic[1,2] and antibiotic properties. From the structural point of view, rotations about the C—S, S—N and N—C bonds are possible in sulphonanilides, and IR spectroscopy has been widely used to study this rotational isomerism.[3–5] The crystal structure of the methanesulphonanilide molecule was determined by Klug[6] using x-ray studies, which showed that it takes the *gauche* conformation with regard to the SC, NC and NH bonds in the crystal state, and that pairs of methanesulphonanilide molecules form centrosymmetric dimers through hydrogen bonds. The amine hydrogen thus clearly is projected on one side of the plane of the phenyl group, while the whole methanesulphonyl group is on the opposite side of the plane. Although these studies indicated the conformation of methanesulphonanilide molecules in the solid state, the solution conformations, as well as the all-important electron charge distribution which will significantly affect the properties of these systems, has not been reported. From the electronic point of view there is a strong possibility of nitrogen electron pair donation into the benzene ring by resonance. This contribution, however, would be reduced owing to the presence of the electron-withdrawing methanesulphonyl group.

Substitution of the benzene ring, particularly in the *para* position, is expected to cause further changes in



electron charge distribution within the aromatic ring. An electronic interaction between the sulphonanilide group and the *para* substituent, which takes place through the aromatic ring, can be visualized. Depending on the nature of the substituent, the electron charge distribution at the *ortho,para* positions can therefore increase or decrease in comparison with the parent sulphonanilide. Conversion of these methanesulphonanilides into the corresponding dimethanesulphonanilides is expected to cause a further reduction in the nitrogen lone pair donation into the aromatic ring. In fact, it is now possible that the presence of two methanesulphonyl groups may even cause a net flow of electron density from the aromatic ring towards the methanesulphonanilide groups. The methanesulphonyl group has been shown to be a strong *ortho,para* director in electrophilic aromatic substitutions, while the dimethane-sulphonyl group directs the incoming groups predominantly to the *para* position, but significant amount of *ortho*- and *meta*-isomers are also produced.[7] Although such electronic interactions between various parts of a molecule can be monitored by several chemical and spectrometric methods, the use of ^{13}C NMR spectroscopy[8] has been shown to be a more desirable choice. We therefore decided to examine the ^{13}C NMR chemical shifts in a number of *para*-substituted anilines and their corresponding methane- and dimethane-sulphonanilides. Attempts have been made to explain the observed shifts in terms of electronic and steric interactions

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taking place in these compounds. Although chemical shift changes at both the *ortho* (C-2, 6) and *para* (C-4) positions can, in general, be taken as an indication of resonance interactions, the *para* position is usually believed to provide a more accurate picture of the resonance phenomenon. At the *ortho* position, the chemical shifts are influenced by resonance and by inductive, spatial shielding and anisotropic effects. The aromatic carbon bearing the substituent (C-1), on the other hand, is primarily affected by the electron-withdrawing inductive effect ($-I$) of the substituent. The *meta* carbons (C-3, 5) are also affected by the inductive effect of substituents, but the magnitude of this effect is very small at these carbons.

EXPERIMENTAL

NMR Spectra

Proton decoupled ^{13}C NMR spectra were recorded on a Varian XL-200 spectrometer operating at 50.3 MHz using 10 mm sample tubes. Solutions for the measurement of the spectra were prepared by dissolving 0.5 g of the sample in 2.5 ml of chloroform-*d* containing a few drops of tetramethylsilane (TMS) as an internal reference. The solvent also provided the internal field-frequency lock signal. The other experimental parameters were as follows: spectral width, 11 000 Hz; data points, 32K; pulse width, 4 μs (90° = 20 μs); and number of transients, 5000. Signal assignments were based on considerations of single-frequency off-resonance decoupled spectra, signal intensity measurements and known substituent effects.[9]

Materials

All the methane- and dimethane-sulphonanilides were synthesized from the corresponding anilines using known procedures.[10] Several important modifications were made, however, in order to obtain better yields. Excellent yields were obtained except with very hindered anilines. A generalized procedure for the synthesis of the methane- and dimethane-sulphonanilide of 2,6-dimethylaniline is shown below.

***N*-(2,6-Dimethylphenyl)methanesulphonamide (7).** To a cooled solution of 0.80 ml (10 mmol) of pyridine in 10 ml of dry dichloromethane were added dropwise 1.14 g (10 mmol) of cold methanesulphonyl chloride followed by 1.21 g (10 mmol) of 2,6-dimethylaniline. The solution was refluxed for 12 h under nitrogen. Heating was not required for less hindered amines. To the resulting mixture, 25 ml of cold 10% sodium hydroxide solution were added and the aqueous layer was washed with 50 ml of dichloromethane. Acidification of the aqueous layer with acetic acid resulted in the precipitation of the methanesulphonanilide **7**, which, on crystallization from dichloromethane–diethyl ether, gave 1.30 g (65%) of white crystals (m.p. 127–128 °C).

***N*-(Methylsulphonyl)-*N*-(2,6-dimethylphenyl)methanesulphonamide (14).** To a solution of 0.57 g (5 mmol) of methanesulphonyl chloride in 1 ml of pyridine was added 1.0 g (5 mmol) of the methanesulphonanilide **7**. The resulting mixture was heated at 80 °C for 24 h under nitrogen. The dark brown mixture was diluted with 50 ml of dichloromethane and the organic layer was washed with 25 ml of 10% sodium hydroxide solution (cold) to remove the starting material. The brown organic layer was dried over magnesium sulphate, filtered and the filtrate was then decolorized with charcoal. Removal of the organic solvent under reduced pressure gave white crystals, which, on recrystallization from dichloromethane–diethyl ether, gave 0.58 g (41.7%) of the dimethane-sulphonanilide **14** (m.p. 159–160 °C).

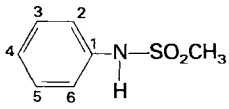
RESULTS AND DISCUSSION

^{13}C Shifts in methanesulphonanilides

In order to understand the results we have compared the chemical shifts in these methanesulphonanilides with those in the corresponding anilines. The results thus show the effect on the chemical shifts of the aromatic carbons of substituting a methanesulphonyl group. The ^{13}C shifts in some methanesulphonanilides, together with their differences from the corresponding anilines, are recorded in Table 1. In all these substituted anilines there is a net resonance flow of electron density from the nitrogen into the aromatic ring. Substitution with a methanesulphonyl group causes a decrease in this interaction, which can be monitored by ^{13}C shift changes at *ortho* (C-2, 6) and *para* (C-4) positions. Thus, as expected, in compounds **1–5** the *para* carbons are deshielded by approximately 5–8 ppm in comparison with the corresponding anilines. In methanesulphonanilide **1**, C-4 is deshielded by 6.8 ppm while in **2** and **3**, where the *para* position is substituted by Cl and CH_3, respectively, the deshielding of this carbon is increased to 8.3 ppm. Apparently, in **2** and **3** the resonance contribution of the sulphonamide nitrogen is decreased. In **4** and **5**, which bear *para*-nitro and *para*-methoxy groups, respectively, the deshielding of the *para*-carbon is reduced to 5.8 and 5.3 ppm, respectively. It is likely that in **4** the strong electron-withdrawing effect of the *para*-nitro group causes an increase in the resonance contribution of the sulphonamide nitrogen. The resonance contribution of nitrogen in **5** is, perhaps, decreased in comparison with **1** because the *para*-methoxy group now effectively competes for resonance contributions of electron density at the *ortho* and *para* positions of the aromatic ring.

The phenomenon of steric inhibition of resonance is demonstrated well in **6**, **7** and **8**. In *ortho*-substituted anilines the amino group, being relatively small, can still take part effectively in resonance with the aromatic ring. However, in *ortho*-substituted methanesulphonanilides, the bulky methanesulphonyl group causes serious steric inhibition of such a resonance.

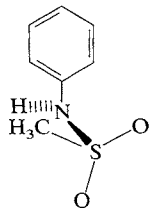
Table 1. ^{13}C chemical shifts (ppm) in some methanesulphonanilides and their differences with the corresponding anilines

Compound		C-1	C-2, 6	C-3, 5	C-4	SO_2CH_3	Others
 **1**		136.7	120.8	129.6	125.3	39.1	
	Δ[a]	−9.8	+5.6	+0.2	+6.8		
2: 4-Cl		135.2	122.1	129.8	131.1	39.4	
	Δ	−10.0	+5.8	+0.8	+8.3		
3: 4-CH_3		134.0	121.5	130.1	135.5	38.9	CH_3 = 20.8
	Δ	−10.3	+6.3	+0.4	+8.3		+0.5
4: 4-NO_2		145.9	119.1	126.3	144.4	40.7	
	Δ	−10.4	+5.2	−1.0	+5.8		
5: 4-OCH_3		129.1	124.6	114.7	157.9	38.6	OCH_3 = 55.5
	Δ	−11.4	+8.3	−0.2	+5.3		0.0
6: 2-CH_3		134.6	131.3 (C-2)	131.1 (C-3)	126.1	39.5	CH_3 = 17.9, Δ = +1.0
	Δ	−9.8	+9.4	+1.0	+7.9		C-5 = 126.9, Δ = +0.3 C-6 = 123.5, Δ = +8.9
7: 2,6-$(CH_3)_2$		132.7	137.3	128.7	127.7	41.5	CH_3 = 19.0
	Δ	−9.7	+16.2	+0.9	+10.3		+2.0
8: *N*-CH_3		141.3	126.1	129.2	127.3	38.0	N—CH_3 = 35.1
	Δ	−7.8	+14.0	+0.3	+10.5		+4.8

[a] Δ = methanesulphonanilide − corresponding aniline.

Thus, in **6**, which bears a methyl group at one of the *ortho* positions, the deshielding of C-4 is increased to 7.9 ppm. The presence of methyl groups at both the *ortho* positions, as in **7**, will cause an even greater steric inhibition of resonance. The *para*-carbon shifts are therefore moved significantly downfield, by as much as 10.3 ppm. The substitution of a methyl group on the nitrogen itself, as in **8**, also causes severe steric inhibition of resonance, and the *para*-carbon is therefore deshielded by 10.5 ppm in this compound. Similar changes in the chemical shifts of *ortho*- and *para*-carbons due to steric inhibition of resonance in several structurally similar systems, such as arylphosphoramidates, have been previously reported.[11]

The chemical shifts of the *ortho*-carbons (C-2, 6) in **1**, **2**, **3** and **4** are downfield by 5–6 ppm in comparison with the corresponding anilines. This is obviously due to the decreased resonance contribution of the nitrogen lone electron pair into the aromatic ring. In addition, the electron-withdrawing inductive effect of the sulphonyl group will also tend to deshield the *ortho*-carbons. The deshielding of the *ortho*-carbons in **5** increases to 8.3 ppm. A probable explanation is that in this compound the *para*-methoxy group effectively contributes to electron density donation into the aromatic ring, thereby reducing the resonance contribution of the sulphonamide group. The C-2 and C-6 positions, which are *meta* to the methoxy group, are unaffected by the resonance contribution of the methoxy group. In **6**, a partial steric inhibition of resonance causes deshielding of C-2 and C-6 by 9.4 and 8.9 ppm, respectively. In **7** and **8**, where a severe steric inhibition of resonance is expected, the deshielding of the *ortho*-carbons is increased to 16.2 and 14.0 ppm respectively. Although steric inhibition of resonance can explain some of the increase in the deshielding of the *ortho*-carbons, perhaps conformational factors are also significant in this regard. In compounds **1**–**5** the preferred conformation of the molecules is such that SC, NC and NH bonds are *gauche* to each other. In this conformation intermolecular hydrogen bonds involving —NH- - - -N— centres are easily formed. The methyl of the methanesulphonyl group is thus spatially close to the *ortho*-carbons of the aromatic ring, and steric crowding will cause shielding of the *ortho*-carbons and of the methyl group. However, in **6** and **7**, which bear methyl groups at *ortho* positions, and in **8**, which bears a methyl group on the nitrogen, rotation around the N—S bond is likely to take place in such a way that severe steric repulsion between the *ortho* substituents and the methanesulphonyl group is minimized. A reduction in the steric crowding will cause downfield shifts for both the *ortho* and the methyl carbons. The preferred conformations in **1** and **7** are shown below as an example.



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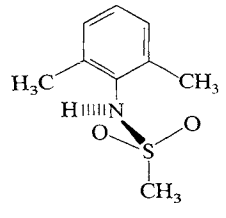

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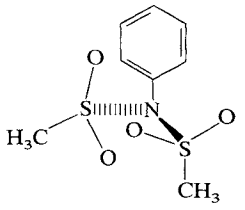
The chemical shifts of C-1 in all these methanesulphonanilides except **5** and **8** are upfield by 9.7–10.4 ppm in comparison with the corresponding anilines. The observation is similar to that noted in other systems, whereby attachment of an electron-withdrawing group on the nitrogen causes a shielding of the aromatic carbon bearing the amino group. Thus,

as an example, the shielding of C-1 in acetanilide is 7.0 ppm in comparison with aniline. The increased shielding of C-1 in **5** (11.4 ppm) may be due to increased participation of the *para*-methoxy group in the resonance process. The chemical shifts of *meta*-carbons (C-3, 5), as expected, are not affected to any significant extent when a methanesulphonyl group is substituted on nitrogen. Thus, in general, the chemical shift of these carbons is downfield by 0.3–1.0 ppm in comparison with the corresponding anilines.

^{13}C shifts in dimethane-sulphonanilides

The ^{13}C shifts in some dimethane-sulphonanilides and their differences from the corresponding methanesulphonanilides are recorded in Table 2. The chemical shift of the *para*-carbon (C-4) can again be regarded as an indicator of the extent of the resonance contribution of electron density from nitrogen into the aromatic ring. Thus, in **9**, the chemical shift of C-4 moves downfield by 5.3 ppm in comparison with the corresponding methanesulphonanilide. Obviously, the substitution of a second methanesulphonyl group causes a further reduction in the resonance contribution of nitrogen. In fact, the chemical shift of this carbon is now even downfield in comparison with benzene. Substitution of the first methanesulphonyl group in aniline (**1**) caused a deshielding of C-4 by 6.8 ppm, while substitution of the second methanesulphonyl group resulted in a smaller deshielding (compared with **1**) of 5.3 ppm. Compounds **10** and **11** show similar deshieldings of 5.8 and 5.4 ppm, respectively. In **12** and **13**, bearing an NO_2 and an OCH_3 group, respectively, at the *para* position, the deshielding is reduced to 4.2 and 3.1 ppm, respectively. This decrease is similar to the results observed in the case of methanesulphonanilides (**4** and **5**) and the reasons are probably the same as given earlier in the discussion. In **14**, bearing methyl groups at both *ortho* positions, the deshielding is unusually small, being reduced to only 2.2 ppm. The reason for the relatively small difference in chemical shifts for all carbons in **14**, when compared with the corresponding methanesulphonanilide **7**, is that there are no significant differences in the nature of the steric and electronic interactions between these compounds. Both compounds experience steric inhibition of resonance, and they also have similar conformations around the N—S bond. All dimethane-sulphonanilides are expected to have a preferred conformation where the methyls in the methanesulphonyl group are directed away from the *ortho* positions of the aromatic ring, i.e.



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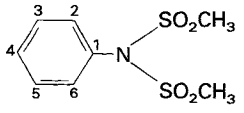
The *ortho*-carbons (C-2, 6) are deshielded by 9.8 ppm in **9** in comparison with the corresponding methanesulphonanilide **1**. As noted previously, the chemical shifts of *ortho*-carbons are affected by several factors, including resonance, inductive and steric effects. Obviously, both the decreased resonance contribution of nitrogen into the aromatic ring, as well as the $-I$ effect of two methanesulphonyl groups, will tend to deshield the *ortho*-carbons. The deshielding of these carbons in **10** and **11**, bearing *para*-chloro and *para*-methyl substituents, respectively, is also of approximately, the same magnitude. However, in **12**, bearing a *para*-NO_2 group, the deshielding of the *ortho* carbons is increased significantly to 12.7 ppm. It may well be that the strong deactivating effect of the nitro group combined with the inability of trisubstituted nitrogen to make an effective resonance contribution leads to this unusually high downfield shift of the *ortho*-carbons. On the other hand, the deshielding of the *ortho*-carbons in **13**, which bears a *para*-methoxy group, is reduced to 7.1 ppm, which

Table 2. ^{13}C chemical shifts (ppm) in some dimethane-sulphonanilides and their differences from the corresponding methanesulphonanilides

Compound		C-1	C-2	C-3	C-4	SO_2CH_3	Others
 **9**		133.4	130.6	129.7	130.6	42.6	
	Δ[a]	−3.3	+9.8	+0.1	+5.3	+3.5	
10: 4-Cl		131.8	131.8	130.0	136.9	42.6	
	Δ	−3.4	+9.7	+0.2	+5.8	+3.2	
11: 4-CH_3		130.7	130.3	130.2	140.9	42.5	CH_3 = 21.2
	Δ	−3.3	+8.8	+0.1	+5.4	+3.6	+0.4
12: 4-NO_2		138.8	131.8	124.8	148.6	42.8	
	Δ	−7.1	+12.7	−1.7	+4.2	+2.1	
13: 4-OCH_3		125.6	131.7	114.9	161.0	42.5	OCH_3 = 55.5
	Δ	−3.5	+7.1	+0.2	+3.1	+3.9	=0.0
14: 2,6-$(CH_3)_2$		132.4	139.6	129.3	129.9	44.0	CH_3 = 19.7
	Δ	−0.2	+2.6	+0.6	+2.2	+2.5	0.7

[a] Δ = dimethane-sulphonanilide − corresponding methanesulphonanilide

may be due to our previously suggested participation of the methoxy group in the resonance process. For reasons given earlier, the *ortho* carbons in **14** are deshielded by only 2.6 ppm, which is small in comparison with the deshielding observed in other dimethane-sulphonanilides. The chemical shift of C-1 in these dimethane-sulphonanilides moves upfield in comparison with the shifts in the corresponding methanesulphonanilides. The magnitude of this upfield shift is approximately 3.5 ppm in **9**, **10**, **11** and **13**. The magnitude of this upfield shift is much smaller than that observed on substituting the first methanesulphonyl group. For example, in **1–7**, the shielding of C-1 is approximately 10.0 ppm. An unusually high upfield shift of 7.1 ppm is observed in **12**, which bears a *para*-nitro group on the aromatic ring. The *meta*-carbons (C-3 and C-5) in these compounds are affected only very slightly in comparison with the corresponding methanesulphonanilides. Thus, in **9**, **10**, **11**, **13** and **14**, the *meta*-carbons move downfield by only 0.1, 0.2, 0.1, 0.2 and 0.6 ppm, respectively. In **12**, however, an upfield shift of 1.7 ppm is observed for these carbons. A study of the ^{13}C chemical shifts has thus provided an important insight into steric and electronic interactions, and the preferred conformations of these compounds.

Acknowledgement

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