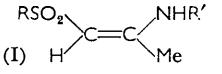
1058. *Long-range Effects in Nuclear Magnetic Resonance. Specific Shielding by Aryl Groups in Some Flexible Systems*

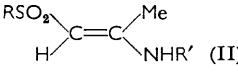
By R. C. Pink, R. Spratt, and C. J. M. Stirling

Shielding by aryl groups at very long range has been detected in the proton magnetic resonance spectra of the adducts (I) and (II) produced by the addition of amines to propargyl sulphones. In one series of adducts, the protons in the flexible chain attached to the nitrogen atom, and separated by six, seven, or eight bonds from it, show different chemical shifts in the *cis*- and *trans*-isomers. The chemical shifts of protons separated by five and nine bonds, however, do not differ. It is suggested that slight conformational differences between the *cis*- and the *trans*-isomers result in preferential shielding, by the aryl group, of protons at specific sites in the chain of the *trans*-isomer. A similar effect is observed in related adducts obtained from acetylenic sulphones and thiols.

Nuclear magnetic resonance spectroscopy has revealed many instances of long-range effects on the screening constants of protons.[1] We now report some extreme examples of this effect, in which protons are shielded by an aromatic nucleus separated by as many as twelve bonds in a flexible structure. The compounds which show this long range effect are obtained [2] by the addition of primary amines to 3-phenylsulphonylpropyne and have the general structures (I) and (II). The adducts consist of equilibrium mixtures of *cis*-(I) and *trans*-forms (II), and it has been shown that in the *cis*-configuration, hydrogen



(I)



(II)

bonding between the amino proton and the sulphonyl group occurs.[2] This hydrogen bond is, in fact, essential for the existence in solution of the *cis*-isomer. Adducts from secondary amines exist only in the *trans*-configuration (cf. III).

[1] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, London, 1959, p. 125.
[2] C. J. M. Stirling, *J.*, 1964, 5863.

While investigating the relationship between the structure of the primary amine and the *cis* : *trans* ratio in the adducts obtained, we examined the p.m.r. spectrum of the mixture of adducts (I and II; R = Ph, R′ = CH_2·CO_2Et) obtained with glycine ethyl ester. Unexpectedly, since the local chemical environment of the ester methyl group appears to be the same in the two species, the signal for this group was found to consist of *two* triplets (Figure 1) separated by 2·1 c./sec. with relative intensities in proportion to the *cis* : *trans* ratio of isomers. The ester methylene group, however, gave the expected simple quartet, and ten-fold reduction of the solute concentration did not alter the methyl-group signal. The spectrum of the adducts (I and II; R = Ph, R′ = CH_2·CO_2Me), obtained from glycine methyl ester, showed a normal singlet for the protons of the ester methyl

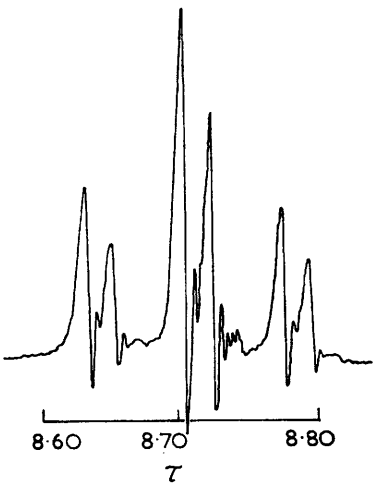
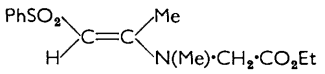
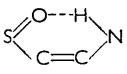


FIGURE 1. Proton magnetic resonance spectrum of the mixture of adducts (I and II; R = Ph, R′ = CH_2·CO_2Et)

group. Clearly, some special factor was responsible for the double methyl signal, and we have investigated this phenomenon with respect to three considerations: (i) the group responsible for the effect, (ii) the distance over which the effect operates, and (iii) the involvement of specific interactions not directly responsible for the effect but nevertheless required for its operation.

(III) 



(IV)

We established first that the doubling of the signal was due to the presence of both isomers in the mixture of adducts; this had already been suspected from the relative intensities of the pair of signals. The adduct (III) obtained from 3-phenylsulphonylpropyne and sarcosine methyl ester, exists in solution as a single isomer, and, according to arguments developed previously,[2] has the *trans* configuration. The signals from the ester methyl and methylene groups were normal.

The presence either of the aryl group or of the sulphonyl group in the adducts appeared to be the likely cause of the differential effect between the isomers. The former was definitely implicated in two ways. The signals for both the ester methyl and methylene groups were both double in the adduct mixture (I and II; R = $PhCH_2$, R′ = CH_2·CO_2Et) obtained from 3-benzylsulphonylpropyne and glycine ethyl ester. As the relative position of the sulphonyl group is unchanged by substitution of benzyl for phenyl, this group cannot be responsible for the observed effect. In confirmation of this conclusion, the adduct mixture (I and II; R = Bu^t, R′ = $[CH_2]_3$·OMe) showed a single signal for the protons of the *O*-methyl group whereas the signal for this group is double in the adducts with R = Ph (below).

The section of the chain R′ which is affected by the aryl nucleus was delineated by examination of the series of compounds (R = Ph) listed in Table 1. The effect is greatest upon protons separated by six bonds from the amino nitrogen atom. At this position, the mean separation between the signals from the *cis*- and *trans*-isomers is 3·2 c./sec. and falls to 2·0 c./sec. for a separation of seven bonds and to 1·0 c./sec. for a separation of eight

TABLE 1

Signal separation, between *trans*- and *cis*-adducts, of protons located in the amino-chain, R′

Adducts (I) and (II)			$\delta\nu$ (*trans–cis*) (c./sec.)				
R	R′	No. of bonds from N:	5	6	7	8	9
Ph	CH_2·CO_2Me		0	—	—	—	—
Ph	CH_2·CO_2Et		0	2·1	—	—	—
Ph	$[CH_2]_2$·CO_2Me		—	3·3	—	—	—
Ph	$[CH_2]_2$·CO_2Et		—	4·7	2·1	—	—
Ph	$[CH_2]_3$·OMe		—	3·6	—	—	—
Ph	$[CH_2]_4$·CH_3		*	3·1	—	—	—
Ph	$[CH_2]_5$·CH_3		*	*	2·2	—	—
Ph	$[CH_2]_7$·CH_3		*	*	*	*	0
Ph	$[CH_2]_3$·CO_2Et		—	—	1·7	1·0	—
$PhCH_2$	CH_2·CO_2Et		4·1	2·1	—	—	—
Me_3C	$[CH_2]_3$·OMe		—	0	—	—	—

* Signal part of broad multiplet.

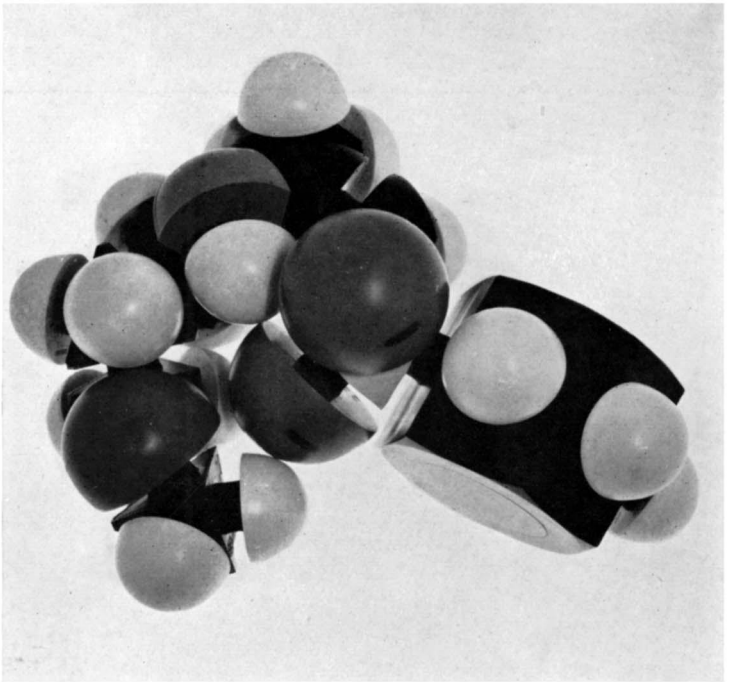
bonds. No effect is observed ($\Delta\nu < 0{\cdot}5$ c./sec.) for a separation of five bonds or of nine bonds. Observation of a double signal for the protons of the *O*-methyl group in the adduct mixture (I and II; R = Ph, R′ = $[CH_2]_3$·OMe), and for the terminal methyl groups in the adducts (I) and (II) (R′ = $[CH_2]_4$·CH_3 and $[CH_2]_5$·CH_3, respectively), demonstrates that the ester function present in the other adducts studied is not essential for this long-range effect to manifest itself.

In each adduct mixture, the *cis*-isomer predominates to the extent of about 60%, and it is the less intense signal, due to the *trans*-isomer, which appears upfield when doubling of the signal is observable. We therefore consider that the doubling of the signal given by protons separated by six, seven, and eight bonds from the nitrogen atom of the flexible chain is due to the different situation of these protons in each isomer with respect to the aryl nucleus.

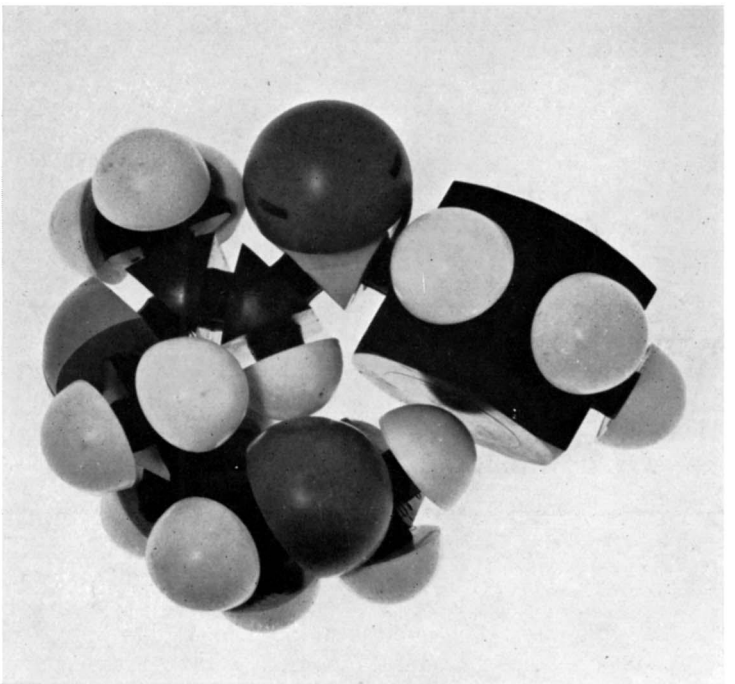
According to the ring-current theory based on a classical free electron model,[3] the effect of a benzene nucleus upon a proton near to it is to produce a negative contribution to the screening constant when the proton is specifically in the same plane as that of the aryl nucleus. On the other hand, a proton in a position directly above the ring should be subjected to a magnetic field from the aromatic ring current opposite in direction to that experienced by the aromatic protons. Its resonance signal should, therefore, be displaced to higher field as a result of the increased shielding. The effect we observe is a time-average differential effect between the isomers, and it appears more probable that preferential shielding of the *trans*-isomer is operative rather than deshielding of the *cis*-isomer.

Since the aromatic nucleus is essentially disc-shaped, there is a greater probability that a group connected to the aromatic nucleus by a long flexible chain will lie above or below the plane of the ring rather than in the plane. Preferential shielding in the *trans*-isomer implies, therefore, that on average the flexible chain approaches the aryl nucleus more closely in the *trans*- than in the *cis*-isomer. Normally this would not be the case but we believe that hydrogen bonding between the amino proton and the sulphonyl group [2] restrains the approach of the side-chain of the *cis*-isomer towards the aryl nucleus because rotation about the S–C= and =C–N bonds is restricted (cf. IV). A lesser degree of flexibility is thus imposed upon the *cis*-isomer. Examination of models confirms this conclusion (Figure 2).

[3] J. A. Pople, *J. Chem. Phys.*, 1956, **24**, 1111.



(*a*)



(*b*)

FIGURE 2. Models of (*a*) *cis*- (hydrogen-bonded), and (*b*) *trans*-2-(3-methoxypropylamino)-1-phenylsulphonylpropene, showing conformations in which the *O*-methyl group is closest to the aryl nucleus

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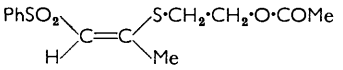
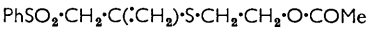
A similar differential effect is revealed in the p.m.r. spectra of the sulphides (V) and (VI). These isomers were obtained by base-catalysed addition of 2-hydroxyethanethiol to 1- and 3-phenylsulphonylpropyne, respectively, and subsequent acetylation of the adducts.



(V)



(VI)

The isomer (V) is assigned the *cis* configuration on the basis of previous investigations.[4] The methyl protons of the ester group of (V) give a single absorption line 7 c./sec. upfield from that given by the corresponding protons of the isomer (VI). In the isomer (V), the flexible chain is held nearer, on average, to the benzene nucleus than in the isomer (VI) in which there is free rotation about the SO_2C–CS bond.

Experimental

The light petroleum used had b. p. 40—60°. Dichloromethane was washed with saturated aqueous sodium hydrogen carbonate. Extracts were dried over sodium sulphate.

Reagents.—3-Methoxypropylamine, b. p. 120°, n_D^{20} 1·4178; 1-aminopentane, b. p. 104°, n_D^{20} 1·4115; 1-aminohexane, b. p. 133°, n_D^{20} 1·4180; 1-amino-octane, m. p. 1°, n_D^{19} 1·4297; β-alanine ethyl ester, b. p. 61°/13 mm., n_D^{17} 1·4289 (lit.,[5] b. p. 56—58°/12 mm., n_D^{25} 1·4250); ethyl 4-aminobutyrate, b. p. 80°/13 mm., n_D^{22} 1·4330 (lit.,[6] b. p. 75—78°/12 mm.). The Fischer–Speier method was used to prepare β-alanine methyl ester hydrochloride, m. p. 105° (lit.,[7] 102·5°); sarcosine ethyl ester hydrochloride, m. p. 125—127° (lit.,[8] 126—127°); and ethyl 4-aminobutyrate hydrochloride, m. p. 86° (Found: C, 42·7; H, 8·6. Calc. for $C_6H_{14}ClNO_2$: C, 43·0; H, 8·4%) (lit.,[9] m. p. 72°).

3-Benzylsulphonylpropyne.—Toluene-ω-thiol (12·4 g.) in 2N-methanolic sodium methoxide (50 ml.) was added with stirring during 10 min. to 3-bromopropyne (13·1 g., 1·1 mol.) in methanol (50 ml.). After 1 hr., the mixture was diluted with saturated brine, and extraction with dichloromethane gave *3-benzylthiopropyne* (13·9 g.), b. p. 113°/9 mm., n_D^{20} 1·5745, ν(≡C–H) 3317 cm.$^{-1}$ (Found: C, 74·2; H, 6·3. $C_{10}H_{10}S$ requires C, 74·0; H, 6·2%). The sulphide (9·3 g.) in acetic acid (35 ml.) at 70° was cautiously treated with 30% aqueous hydrogen peroxide (19 ml., 4 mol.). When addition was complete, the mixture was kept at 100° for 45 min. Addition of water gave the *sulphone* (9·5 g.), m. p. 108—109° (from methanol) (Found: C, 62·1; H, 5·3. $C_{10}H_{10}O_2S$ requires C, 61·9; H, 5·5%).

3-t-Butylsulphonylpropyne.—This compound was obtained by a procedure similar to that used for the previous compound. *3-t-Butylthiopropyne* (61%) had b. p. 63°/37 mm., n_D^{20} 1·4778, ν(≡C–H) 3225 cm.$^{-1}$ (Found: C, 65·6; H, 9·4. $C_7H_{12}S$ requires C, 65·6; H, 9·4%). Oxidation as before gave the *sulphone* (43%), m. p. 98—99° (from di-isopropyl ether) (Found: C, 52·5; H, 7·4. $C_7H_{12}O_2S$ requires C, 52·5; H, 7·5%).

General Procedure for the Preparation of Amine Adducts.—A vigorously stirred solution of the acetylenic sulphone (500 mg.) in methanol (5 ml.) was treated with the amine (1·1 mol.) or with the amine hydrochloride (1·1 mol.) and triethylamine (1·1 mol.). When the free amine was used, evaporation of the mixture after 24 hr. yielded the adduct directly. When the hydrochloride was employed, the mixture was diluted with water and extraction with dichloromethane yielded the product.

The adduct from 3-phenylsulphonylpropyne and ethyl 4-aminobutyrate did not crystallise and could not be distilled without decomposition. The specimen for p.m.r. examination was obtained from equimolecular amounts of sulphone and amino-ester; the spectrum obtained was entirely consistent with the assigned structure. The adducts (I and II; R = Ph, R′ = $CH_2{\cdot}CO_2Me$ and $CH_2{\cdot}CO_2Et$) were described [2] earlier; details of the others are given in Table 2.

[4] C. J. M. Stirling, *J.*, 1964, 5856.
[5] J. Wyman and T. L. McMeekin, *J. Amer. Chem. Soc.*, 1933, **55**, 915.
[6] E. Merck, G.P. 597,305 (1931).
[7] K. Morsch, *Monatsh.*, 1933, **63**, 220.
[8] E. A. Prill and S. M. McElvain, *J. Amer. Chem. Soc.*, 1933, **55**, 1233.
[9] A. Neuberger, *Proc. Roy. Soc.*, 1937, *A*, **158**, 68.

TABLE 2

Amine–sulphone adducts (I), (II), and (III)

R	R′	M. p.	Yield (%)	Reqd. (%) C	Reqd. (%) H	Formula	Found (%) C	Found (%) H
Ph	$[CH_2]_2{\cdot}CO_2Me$	124—125°	90	55·1	6·0	$C_{13}H_{17}NO_4S$	55·1	6·0
Ph	$[CH_2]_2{\cdot}CO_2Et$	63—64	95	56·5	6·4	$C_{14}H_{19}NO_4S$	56·3	6·3
Ph	$[CH_2]_3{\cdot}OMe$	86—87	96	58·0	7·1	$C_{13}H_{19}NO_3S$	57·9	7·2
Ph	$[CH_2]_4{\cdot}CH_3$	88—89	94	62·9	7·9	$C_{14}H_{21}NO_2S$	62·8	8·1
Ph	$[CH_2]_5{\cdot}CH_3$	47·5—48·5	87	64·1	8·2	$C_{15}H_{23}NO_2S$	63·8	8·15
Ph	$[CH_2]_7{\cdot}CH_3$	58—59	90	66·0	8·75	$C_{17}H_{27}NO_2S$	66·0	8·8
CH_2Ph	$CH_2{\cdot}CO_2Et$	64—66	76 *	56·5	6·4	$C_{14}H_{19}NO_4S$	56·65	6·4
Me_3C	$[CH_2]_3{\cdot}OMe$	63—64	70 †	53·0	9·2	$C_{11}H_{23}NO_3S$	53·0	9·4
(III)		63—63·5	65	56·5	6·4	$C_{14}H_{19}NO_4S$	56·5	6·3

* Recryst. from benzene–di-isopropyl ether. † Recryst. from di-isopropyl ether.

Unless otherwise stated, all adducts were purified by crystallisation from benzene–light petroleum to constant m. p.

cis-2-(2-*Acetoxyethylthio*)-1-*phenylsulphonylpropene* (V).—1-Phenylsulphonylpropyne [4] (1 g.) and 2-hydroxyethanethiol (434 mg., 1·05 mol.) in methanol (10 ml.), were treated with triethylamine (0·1 ml.). After 1 hr., the mixture was evaporated, and the residue, which did not crystallise, was treated with acetic anhydride (2 ml.) in pyridine (5 ml.). After 2 hr., water was added and the mixture was extracted with dichloromethane. The extracts were washed successively with 2N-hydrochloric acid (2 × 100 ml.) and saturated aqueous sodium hydrogen carbonate. Evaporation of the extracts gave the *acetate* (1·19 g.), m. p. 108—110° (from benzene–light petroleum) (Found: C, 52·05; H, 5·3. $C_{13}H_{14}O_4S_2$ requires C, 52·0; H, 5·3%).

2-(2-*Acetoxyethylthio*)-3-*phenylsulphonylpropene* (VI).—Treatment of 3-phenylsulphonylpropyne with 2-hydroxyethanethiol and subsequent acetylation of the adduct as above gave the acetate (92%), m. p. 46—47° (from benzene–light petroleum) (Found: C, 52·1; H, 5·35%).

Proton Magnetic Resonance Spectra.—Spectra were obtained using a Varian HR-100 spectrometer operating at 100 Mc./sec. Except where otherwise stated, 10% w/v solutions in deuterochloroform were used at *ca.* 31°, with tetramethylsilane as internal standard. Assignments were verified when necessary by spin decoupling.

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