Hydrogen Bonds involving Polar CH Groups. Part 10.[1] Intramolecular Hydrogen Bonds in 1-(ω-Substituted-alkyl) Bis(phenylsulphonyl)methanes

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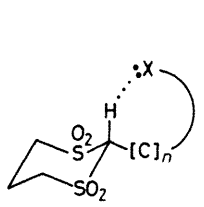
Intramolecular hydrogen bonds involving the polar methine group have been detected by ^{1}H n.m.r. spectroscopy in dichloro[$^2H_2$]methane in 1-(ω-methoxyalkyl)- and 1-(ω-dialkylaminoalkyl)-bis(phenylsulphonyl)methanes. Dialkylamino groups are more effective donors than methoxy, and interactions are maximised when a five- or ideally a six-membered ring can be formed. The optimum compounds, having a methyl group in the side-chain to reduce conformational mobility, show ^{1}H n.m.r. downfield shifts of *ca.* 1.9 p.p.m. relative to a reference compound, increasing to 2.2 p.p.m. on lowering the temperature to −40 °C. Downfield shifts are generally larger than for similarly substituted 1,3-dithiane 1,1,3,3-tetraoxides; the phenyl groups appear to reduce further the conformational mobility of the side-chain. Interactions are uncoupled partly by acetonitrile and pyridine, and fully by trifluoroacetic acid. Some i.r. evidence for an interaction is also presented.

In Part 9 of this series we demonstrated that intramolecular interactions as shown in structures (1) existed for dichloro-[$^2H_2$]methane solutions of compounds having $n = 2$ or 3, and X = OMe or NR_2.[1] Interactions were identified by a downfield shift in the ^{1}H n.m.r. signal for the disulphone methine proton relative to that for compounds having X = Pr^i. Shifts when X = NR_2 were greater than for X = OMe, the most effective donor group being piperidino. The optimum compound (2), which had a side-chain methyl group to reduce conformational mobility, showed a methine-signal downfield shift of 2.15 p.p.m. relative to a reference compound, thus demonstrating a strong interaction of the hydrogen-bonding type. Interactions were uncoupled in deuteriated acetonitrile and by pyridine due to competition for the methine proton by the solvent, and by trifluoroacetic acid (TFAA) due to protonation of the group X.

X-Ray crystallographic data for bis-(4-bromophenylsulphonyl)methane show it to exist in a W-shaped conformation,[2] although dipole-moment studies on closely related compounds suggest that this is not necessarily the form adopted in solution.[3,4] It nevertheless seemed that the phenyl groups in structures of type (3) might further reduce conformational mobility in the side-chain, enhancing any intramolecular interaction relative to analogues (1). Additionally, such structures should be amenable to methine H–D exchange, permitting the effect of H-bonding on ν_{C-D} in the i.r. spectrum to be determined. Similar experiments with structures (1) had been inconclusive due to concomitant H–D exchange at the ring C-4 and C-6 methylene groups.[5]

Intermolecular hydrogen bonds between the polar methylene group in the disulphone (4), and both dimethyl sulphoxide and pyridine have been reported recently;[6] intramolecular hydrogen bonds involving polar CH groups have received scant attention, and few authentic examples are known. We now describe the preparation of a series of 1-substituted bis-(phenylsulphonyl)methanes, and present further evidence for intramolecular hydrogen bonding from n.m.r. and i.r. spectra.



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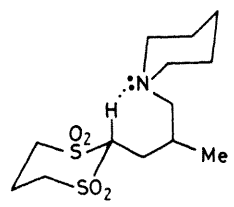

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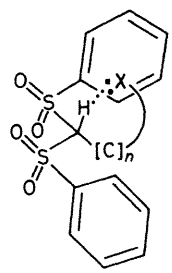

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Results and Discussion

Preparation of the Compounds.—Treatment of the disulphone (4) with sodium hydride in dry dimethylformamide (DMF), followed by the addition of bifunctional compounds (5; Y = Cl, Br) gave the derivatives (6) and (7) (Scheme). Similar alkylation of compound (4) has been reported elsewhere.[7,8] Amino compounds (8)—(11), and the side-chain-methyl derivatives (13) and (14) were obtained similarly from the appropriate chloroamine hydrochlorides, only using an extra mole of sodium hydride. An attempt to prepare, from 1,4-dibromobutane, the bromide (12c), as a precursor to the piperidino derivative (11c), led instead to the cyclopentane (15). This reaction is analogous to the preparation of spiro-1,3-dithiane 1,1,3,3-tetraoxides.[1]

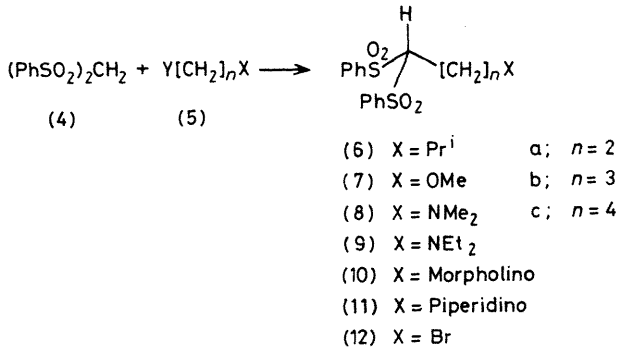
In contrast to the syntheses of many compounds (1),[1] the analogues (3) all required strictly non-protic conditions. Use of sodium methoxide in methanol as base, for example, resulted only in recovery of unchanged disulphone (4). The pK_a of compound (4) in protic solvents (11.2 [9]) is significantly lower than that for 1,3-dithiane 1,1,3,3-tetraoxide (12.61[10]); the reactivity of the carbanion would be further decreased both by solvation with methanol and by the steric effect of the phenyl groups.

Most compounds prepared had $n = 2$ or 3, since these were the chain lengths for which intramolecular interactions (five- and six-membered ring, respectively) were most likely to be observed.[1]

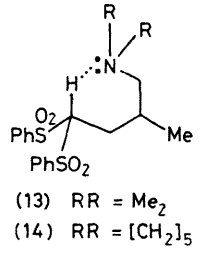
Table 1. Preparative, physical, and analytical data for bis(phenylsulphonyl)methanes

Compound	Yield (%)	M.p. (°C)	Solvent [a]	Found (%) [Required] C	H	N (S)	Formula
(6a)	75	137	I	59.3 [59.0	5.9 6.05	(17.5) (17.5)]	$C_{18}H_{22}O_4S_2$
(7a)	58	119	I	54.1 [54.2	5.3 5.1	(17.9) (18.1)]	$C_{16}H_{18}O_5S_2$
(7c)	66	70	I	56.6 [56.5	5.7 5.8	(16.5) (16.8)]	$C_{18}H_{22}O_5S_2$
(8a)	63	124	I	55.8 [55.6	6.0 5.8	3.85 3.8]	$C_{17}H_{21}NO_4S_2$
(8b)	68	92	I	56.7 [56.7	6.1 6.1	3.4 3.7]	$C_{18}H_{23}NO_4S_2$
(9a)	77	94	I	57.7 [57.5	6.4 6.2	3.5 3.7]	$C_{19}H_{25}NO_4S_2$
(10a)	82	147	II	55.8 [55.7	5.7 5.7	3.4 3.4]	$C_{19}H_{23}NO_5S_2$
(11a)	57	125	I	58.9 [58.9	6.1 6.2	3.3 3.4]	$C_{20}H_{25}NO_4S_2$
(11b)	65	95	I	60.0 [59.9	6.6 6.5	3.3 3.3]	$C_{21}H_{27}NO_4S_2$
(13)	72	99	I	57.7 [57.6	6.4 6.2	3.5 3.3]	$C_{19}H_{25}NO_4S_2$
(14)	57	128	I	60.7 [60.7	6.5 6.7	3.1 3.2]	$C_{22}H_{29}NO_4S_2$
(15)	88	149	III	58.1 [58.3	5.3 5.2	(18.3) (18.3)]	$C_{17}H_{18}O_4S_2$

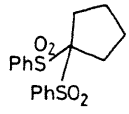
[a] I Benzene–light petroleum (b.p. 80—100 °C) (1 : 1); II Benzene; III $CHCl_3$–CCl_4 (1 : 1).



Scheme. *Reagents and conditions:* NaH, DMF, 80 °C



(13) RR = Me_2
(14) RR = $[CH_2]_5$



(15)

Preparative, physical, and analytical data for some of the compounds (6)—(11) and for (13)—(15) are given in Table 1; no attempt was made to optimise yields. Most disulphones showed a parent ion and a prominent $M - 1$ peak in their mass spectra; in the i.r. there were bands at *ca.* 1 340 and 1 150 cm^{-1} characteristic of the SO_2 groups, and at *ca.* 760 and 695 cm^{-1} due to the phenyl rings. N.m.r. signals arising from the methine function are discussed in the next section; aryl protons absorbed in the range δ_H 7.5—8.0, and aryl carbon atoms at δ_C *ca.* 138.8 (C-1), 129.7 [C-2 and -6; diastereotopic in structures (13) and (14)], 129.5 (C-3 and -5), and 134.7 p.p.m. (C-4).

Evidence for Intramolecular Interactions.—N.m.r. data for the potentially H-bonding methine group in bis(phenylsulphonyl)methanes, recorded under a variety of conditions, are shown in Table 2. Also included, in parentheses for comparison purposes, are data from identically substituted compounds (1), taken from ref. 1. Solvents selected were also those of ref. 1, justified by experience: dichloro[$^2H_2$]methane for observing, and [$^2H_3$]acetonitrile, pyridine, and TFAA for uncoupling, any intramolecular interactions. Selected spectra were recorded for solutions 1.6×10^{-2}M in dichloro[$^2H_2$]-methane; no changes were observed in chemical shifts, showing negligible intermolecular interaction between sulphone molecules.

^1H *N.m.r. data.* The methine chemical shift for the isopentyl compound (6a) may be taken as a reference standard under each set of conditions, since it will not be influenced by intramolecular interactions. Its value in dichloro[$^2H_2$]methane (δ 4.35) compares well with values (δ 4.34, 4.36; $CDCl_3$) for two closely related compounds.[8] Trends in chemical shifts are in general parallel to those observed for compounds (1),[1] but with some important differences in detail.

(*a*) In dichloro[$^2H_2$]methane, intramolecular interactions are apparent, as was found for compounds (1), from a downfield shift in the methine proton signal in all methoxy- and dialkylamino-compounds studied. The magnitudes of these shifts ($\Delta\delta$) relative to compound (6a) are the significant feature; they are again found to be larger for dialkylamino- than for methoxy-substituents, showing the former to be the better donors. In addition, all dialkylamino compounds having $n = 3$ show an appreciable increase in $\Delta\delta$ on lowering

Table 2. N.m.r. data (^1H and ^{13}C) [a] for the potential proton-donor site in bis(phenylsulphonly)methanes [b]

Compd.	Terminal substituent (X)	Chain length (*n*)	δ (^1H) CD_2Cl_2 −40 °C	CD_2Cl_2 20 °C	CD_3CN 20 °C	Pyridine [c] 0.20 ml	Pyridine [c] 0.45 ml	TFAA [d] 0.1 ml	TFAA [d] 0.3 ml	δ (^{13}C) CD_2Cl_2 20 °C	$^1J_{CH}$ (Hz)
(6a)	Pr^i	2	4.39	4.35	4.76	5.14	5.38	4.66	4.73	84.16	143.6
			(4.26)	(4.18)	(4.51)	(4.79)	(4.90)	(4.50)	(4.58)	(80.60)	(147.5)
(7a)	OMe	2	4.87	4.80	4.90	5.24	5.38	4.97	5.08	79.88	145.5
			(4.67)	(4.57)	(4.75)	(4.97)	(5.10)			(77.17)	(150.5)
(7c)	OMe	4	4.53	4.48	4.77	5.23	5.41	4.61	4.72	83.81	143.5
			(4.31)	(4.23)	(4.54)	(4.85)	(5.00)			(80.41)	(148.9)
(8a)	NMe_2	2	5.22	5.19	5.22	5.48	5.61			79.96	144.5
			(4.94)	(4.86)	(4.88)	(5.07)	(5.22)			(77.17)	(147.3)
(8b)	NMe_2	3	5.46	5.20	5.25	5.56	5.76	4.80	4.90	82.69	144.5
			(4.65)	(4.62)	(4.68)	(4.95)	(5.07)	(4.60)	(4.66)	(80.40)	(143.8)
(9a)	NEt_2	2	5.26	5.15		5.40	5.54			80.27	144.4
			(4.99)	(4.86)		(5.14)	(5.45) [e]			(77.62)	(145.2)
(10a)	Mor [f]	2	5.30	5.21	5.25	5.40	5.55			79.83	144.0
			(4.96)	(4.84)	(4.94)	(5.26)	(5.56) [e]			(77.43)	(148.4)
(11a)	Pip [g]	2	5.39	5.31	5.30	5.60	5.74			80.05	142.6
			(4.97)	(4.88)	(4.93)	(5.25)	(5.50) [e]			(77.71)	(145.7)
(11b)	Pip [g]	3	5.46	5.22	5.28	5.45	5.60	4.86	4.98	82.86	145.0
			(5.08)	(5.03)	(4.86)	(5.24) [d]	(5.35) [d,e]	(4.65)	(4.75)	(80.26)	(145.2)
(13)	NMe_2	3	6.57	6.22	6.00	6.18	6.29	4.70	4.72	80.48	142.1
						6.25 [d]	6.31 [e]				
			(5.64)	(5.53)	(5.07)	(5.60) [d]	(5.61) [d]	(4.65)	(4.70)	(78.12)	(147.0)
(14)	Pip [g]	3	6.49	6.24	6.06	6.10 [d]	6.23 [d]	4.60	4.72	80.93	145.6
			(6.77)	(6.40)	(5.53)	(5.95) [d]	(5.97) [d,e]	(4.61)	(4.70)	(77.96)	(144.2)

[a] Relative to internal Me_4Si; solutions 3.2 × 10^{-2}M unless otherwise indicated. [b] Data in parentheses are for identically substituted 1,3-dithiane 1,1,3,3-tetraoxides, and are from ref. 1. [c] Volume added to 0.25 ml of a 0.5M-CD_3CN solution. [d] Volume added to 0.25 ml of a 0.5M-CD_2Cl_2 solution. [e] 0.75 ml added. [f] Morpholino. [g] Piperidino.

the temperature; in the cyclic disulphone series, only the optimum compound (2) showed this effect.[1] Values of Δδ are also larger at both temperatures for all bis(phenylsulphonyl)-methanes relative to analogues (1), with the exception of compound (14); the increase is especially noticeable for the dimethylamino derivatives (8b) and (13).

Since the observed methine chemical shift is a weighted average of contributions from all conformations adopted by a given molecule, the increase in Δδ in the bis(phenylsulphonyl)-methanes can be rationalised in terms of a greater contribution from the H-bonding conformation (3), enhanced further at lower temperatures when $n = 3$. This is consistent with a reduction in conformational mobility of the substituted alkyl chain, brought about by the two bulky phenyl groups. Shifts in the range 0.80—2.18 p.p.m. suggest very significant intramolecular interactions, optimised as with compounds (1) by a side-chain 2-methyl substituent.

For compounds (1) having $n = 3$, by far the most effective donor group was piperidine; [1] in the bis(phenylsulphonyl)-methane series, dimethylamino and piperidino are comparable. This arises because the large increases in Δδ for derivatives (8b) and (13), relative to analogues (1), are not found in the piperidino compounds (11b) and (14). Instead, with compound (11b) there is only a small increase, while with compound (14) Δδ actually decreases. We believe that the two phenyl substituents, while reducing conformational mobility in the side-chain, also sterically hinder the approach of the more bulky piperidino group to the methine.

The ^1H n.m.r. spectra of compounds (6a) and (14) are compared in the Figure.

(*b*) Changes in the methine chemical shift on changing the medium (Table 2) again follow the pattern of ref. 1. In $[^2H_3]$acetonitrile, or on adding pyridine, the observed chemical shift reflects competition between the basic solvent and the donor group X for co-ordination to the methine proton; also, possibly, other solvent-induced anisotropic effects. From the data for compound (6a), pyridine is seen to cause the larger (incremental) downfield shift of the two.* Changes in chemical shift, relative to values in dichloro$[^2H_2]$methane, are seen to be small for solutions of amino compounds in $[^2H_3]$acetonitrile, and generally smaller than changes for comparable cyclic disulphones (1), especially in the case of compounds (11b), (13), and (14). This is consistent with a larger formation constant for the intramolecular interactions in the bis-(phenylsulphonyl)methanes. A similar pattern is observed for pyridine addition, allowing for the larger shift caused by this solvent.

On adding TFAA, the effect on compound (6a) is a shift to lower field by the methine signal, reflecting the solvent anisotropy, and possibly protonation at the sulphonyl groups. Amino compounds all show a large shift to *high* field, consistent with uncoupling of intramolecular interactions; then a shift towards lower field on further addition, reflecting an increasing concentration of the protonated form.

^{13}C *N.m.r. data.* As with compounds (1), neither δ (^{13}C) nor $^1J_{CH}$ appear to be sensitive to the observed intramolecular interactions (Table 2). All δ values, with the exception of those for compounds (6a) and (7c), lie 2.6 ± 0.4 p.p.m. to lower field than those for the corresponding analogues (1). The value for (6a) agrees closely with reported shifts (δ 83.4, 83.9) [8] for two related alkyl derivatives.

From i.r. spectra by H–D *exchange.* Several compounds (1), including the optimum compound (2), after being stirred with deuterium oxide in acetone, showed three absorptions in the ν_{C-D} region: respectively at 2 240 ± 2, 2 191 ± 2, and 2 160 ± 2 cm^{-1}; exchange of C-2, C-4, and C-6 ring protons had occurred.[5] Similar treatment of compounds (6a) and (13), in

* The reason for this is given in ref. 1. Solvent shifts for compound (6a) are larger than for 2-isopentyl-substituted (1).

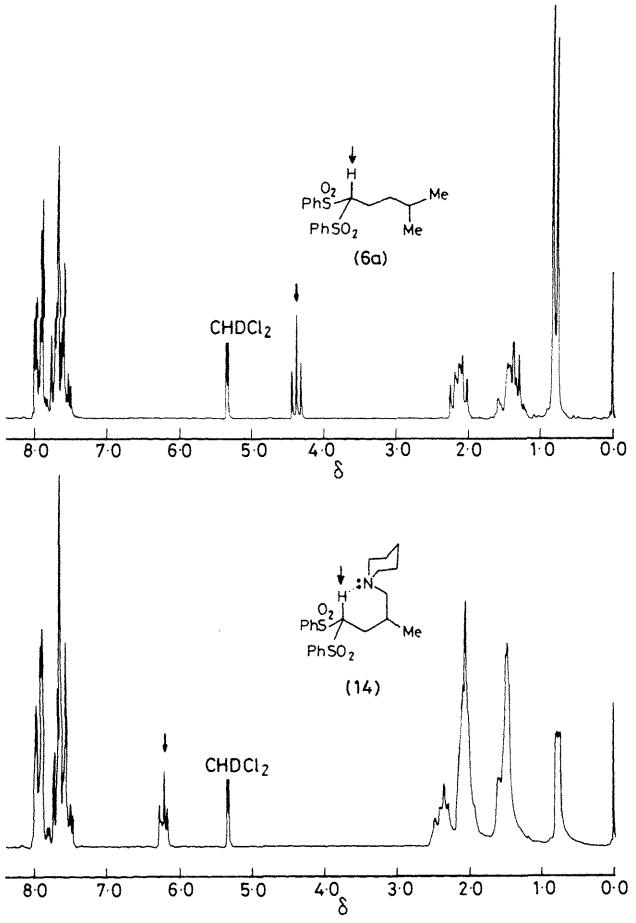


Figure. ^{1}H N.m.r. spectra of compounds (6a) and (14) in dichloro-[$^2H_2$]methane. The methine signal is indicated with an arrow

which only exchange at the methine of interest is possible, gave products showing only one ν_{C-D} absorption, respectively at 2 162 ± 2 and 2 150 ± 2 cm^{-1} for the two compounds, both in Nujol and in solution in *cis*-1,2-dichloroethene. The shift to lower frequency by 10 cm^{-1} in compound (13) is supportive evidence for an intramolecular interaction; however, recent work has shown that there is little correlation between i.r. shifts and formation constants for hydrogen bonds with C–H groups.[11]

Experimental

I.r. spectra were recorded in Nujol, unless otherwise stated, on a Perkin-Elmer 577 spectrophotometer; ^{1}H (89.56 MHz; ±0.2 Hz) and ^{13}C (22.50 MHz; ±1.2 Hz) n.m.r. spectra were recorded on a JEOL FX 90Q instrument; mass spectra were run on a Hitachi RMS-4 spectrometer.

The disulphone (4) was prepared by oxidising (H_2O_2–AcOH) [12] the product from sodium benzenethiolate and diiodomethane.[13]

Preparation of Sulphones.—*Compounds* (6a), (7a), (7c), *and* (15). To a solution of the sodium salt of compound (4) [formed from (4) (3.0 g, 0.01 mol) and NaH (0.011 mol) in dry DMF (30 ml)] at 70—80 °C was added a solution of the appropriate alkyl bromide (5) (0.01 mol) in dry DMF (30 ml). After 1 h, the solvent was removed under reduced pressure and the residue was washed with 2M-NaOH (2 × 15 ml) and was recrystallised. 1,4-Dibromobutane gave 1,1-*bis*(*phenylsulphonyl*)*cyclopentane* (15); $M^{\cdot+}$ 350; $\nu_{max.}$ 1 334, 1 320, 1 165, 1 150, 765, and 695 cm^{-1}; δ($CDCl_3$) 8.05 (4 H, m), 7.68 (6 H, m), 2.55 (4 H, m), and 1.75 (4 H, m).

Dialkylamino compounds. A solution of the sodium salt of compound (4) was prepared as above. To this was added dropwise at 70—80 °C a solution prepared from the appropriate *N*,*N*-dialkyl-ω-chloroamine hydrochloride (0.01 mol) and NaH (0.011 mol) in dry DMF (15 ml). After 1 h the solvent was removed under reduced pressure and the residue was washed with 2M-NaOH (2 × 15 ml). It was purified by column chromatography (SiO_2; $CHCl_3$), followed by recrystallisation.

Physical and analytical data are given in Table 1.

Deuterium Exchange.—Pure samples of compounds (6a) and (13) were stirred with D_2O–Me_2CO (1 : 1) at 25 °C for 72 h. The solvent was removed under reduced pressure at 25 °C; i.r. spectra were determined directly.

Acknowledgements

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