Hydrogen Bonds involving Polar CH Groups. Part 9.[1] Optimum Structural Parameters, and Unequivocal Demonstration of such Intramolecular Interactions in 2-Substituted 1,3-Dithian 1,1,3,3-Tetraoxides

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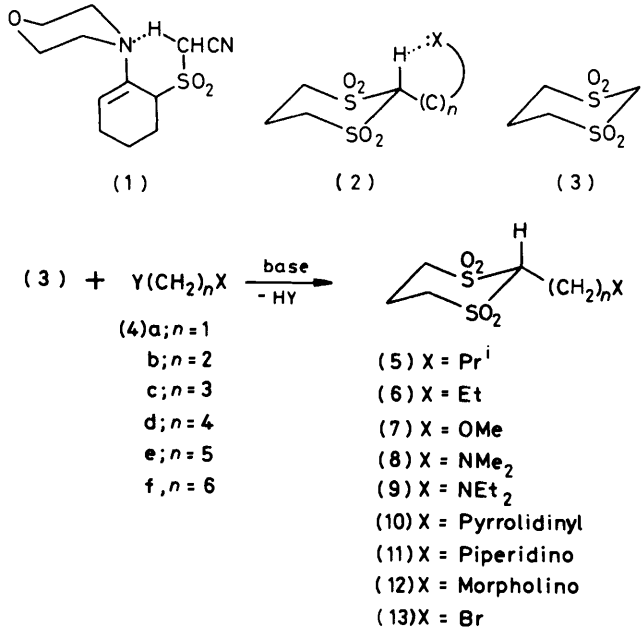
A series of 2-monosubstituted 1,3-dithian 1,1,3,3-tetraoxides have been prepared, having side chains with 2—6 carbon atoms, and bearing alkyl, aryl, methoxy, dialkylamino, and pyridyl terminal substituents, as models for intramolecular C–H · · · X hydrogen bonds. Methoxy- and amino-substituents, in compounds having two or three carbon atoms in the side chain, show significant intramolecular interactions with the disulphone methine hydrogen in [$^2H_2$]dichloromethane, as evidenced by a downfield shift of the ^1H n.m.r. signals; shifts of up to 2.0 p.p.m. have been observed. Intramolecular H-bonds are disrupted in [$^2H_3$]acetonitrile and in pyridine owing to competing intermolecular interactions with the solvents, and in trifluoroacetic acid owing to protonation of the donor atom.

In an earlier paper we produced strong evidence for an intramolecular C–H · · · N hydrogen bond in the nitrile–sulphone (1), both from *X*-ray crystallographic data, and from i.r. and ^1H n.m.r. spectra.[2] Attempts to demonstrate similar interactions in some related molecules, however, were unsuccessful.[3] Although *inter*molecular C–H · · · X hydrogen bonds are well authenticated,[4] and have been the subject of several systematic studies,[5] *intra*molecular interactions of this type have received scant attention. Evidence for the latter has come largely from *X*-ray crystal structures, without supporting spectroscopic data. We thus decided to carry out a systematic study into the effect of varying different structural features in potentially intramolecular H-bonding molecules containing an sp^3-CH group, in the hope of establishing the optimum parameters for such interactions.

Structures of type (2) were selected for the study, since they should be readily accessible from the cyclic disulphone (3), and contain a polar non-enolisable CH group (at C-2) potentially capable of interacting with an electron-donor group X. Structures having X = OMe or NR_2 might show observable intramolecular interactions, while those having X = alkyl or phenyl would serve as reference standards. Further, the length, *n*, of the side chain $(C)_n$ could be varied to establish the optimum ring size for any interaction, and the stereochemistry modified by additional substitution in the chain.

From previous experience,[2,3] ^1H n.m.r. chemical shifts and i.r. C–D stretching frequencies were the spectroscopic parameters of choice for detecting interactions, although the latter have been shown to be unreliable;[5a] the models (2) also permit the parameters δ (^{13}C), $^1J_{CH}$, and $^3J_{HH}$ to be evaluated in this role.



Scheme 1.

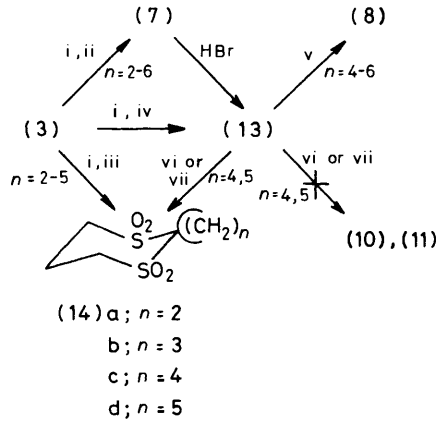
Results and Discussion

Preparation of Compounds.—Few examples of 2-monosubstituted 1,3-dithian 1,1,3,3-tetraoxides have been reported previously.[6-8] The reference compounds (5) and (6), and the methoxy-derivatives (7) (Scheme 1) were readily prepared from the disulphone (3) (pK_a 12.61[9]) † and the appropriate halide (4; Y = Cl, Br) in dimethylformamide, in the presence of methanolic sodium methoxide (method A). Dimethylformamide was used on account of the low solubility of the disulphone (3) in other organic solvents: while the disulphone dissolved readily in aqueous sodium hydroxide, it could not be alkylated in that medium. For the preparation of the dialkylamino-derivatives (8)—(12), the use of the hydrochloride salt of the appropriate halogeno-amine (4; X = NR_2) together with an extra mole of base led successfully to compounds (8b) and (8c), (9b) and (9c), (11b) and (11c), and (12b) and (12c), but failed in all other cases owing to competing intra- and inter-molecular reactions of the halogeno-amines (4).‡ Derivatives (10b) and (10c) were prepared successfully, however, using sodium hydride (method B) in place of methanolic sodium methoxide, alkylation of the disulphone anion presumably occurring faster in the absence of the solvating methanol.

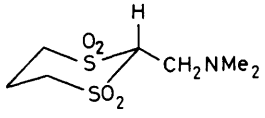
For amino-derivatives having *n* = 4—6, alternative approaches were explored (Scheme 2), the most attractive being the reaction between bromo-compounds (13) and a secondary amine (method C). Although 1,6-dibromohexane gave the

† In non-protic media this value becomes >15 (F. G. Bordwell, J. C. Branca, D. L. Hughes, and W. N. Olmstead, *J. Org. Chem.*, 1980, **45**, 3305).

‡ This was also a problem when alkylations of lithio-1,3-dithian, were attempted with the same halogeno-amines in tetrahydrofuran.



Scheme 2. *Reagents:* i, base; ii, $Br(CH_2)_nOMe$; iii, $Br(CH_2)_nBr$; iv, $Br(CH_2)_6Br$; v, Me_2NH; vi, pyrrolidine; vii, piperidine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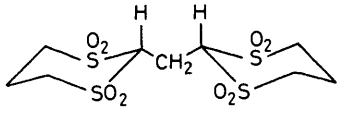
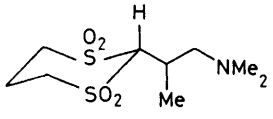

(15)

bromide (13f) by method A, all other dihalides reacted further to yield the spiro-compounds (14) together with unchanged sulphone (3). The structures of the spiro-sulphones were confirmed from spectroscopic data (see Experimental section); (14b) and (14c) are novel, while (14a) [10] and (14d) [11] have been reported previously. The bromides (13d) and (13e) were subsequently obtained by cleavage of the ethers (7d) and (7e) with hydrobromic acid (method D), and together with (13f) were converted smoothly into the amines (8d—f) on reaction with dimethylamine. Both pyrrolidine and piperidine, however, gave the spiro-compounds (14) rather than the desired amines (10) and (11). The reaction between the disulphone (3), formaldehyde, and dimethylamine under a variety of conditions gave the known [12] bis-disulphone (15) rather than compound (8a).

The flexibility of the side chain $(C)_n$ in structures (2) may be decreased, and hence the stereochemistry of a possible intramolecular interaction controlled to some extent, either by introducing alkyl substituents into the side chain, or by incorporating part of the chain and the substituent X into a ring (saturated or unsaturated). Attempted preparation of compound (16) from 2-chloro-*N*,*N*-dimethylpropanamine by method B gave instead the isomer (17), formed apparently from attack of the disulphone anion at the least-hindered carbon atom of the intermediate 1,1,2-trimethylaziridinium cation. A similar reaction using 3-chloro-2,*N*,*N*-trimethylpropanamine led smoothly to compound (18): the piperidino-analogue (19) was prepared similarly, while the dimethyl-compound (20) was synthesised as reported recently.[1]

For compounds having part of the chain in a ring, the pyrrolidine derivative (21) was prepared by method A, but all attempts to synthesise the piperidine compounds (22) and (23) failed owing to competing intramolecular fragmentation reactions of the precursor chloropiperidines.[13] The pyridine derivative (25), having an sp^2-nitrogen as a potential electron donor, was also prepared successfully by method A, as were the reference compounds (24) and (26).

Generally, no attempt was made to optimise the yields, but in the few cases where this was done yields >70% were obtained. Preparative, physical, and analytical data are given in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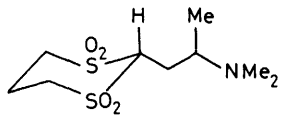
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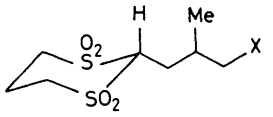
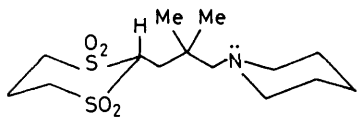

(18) X = NMe_2
(19) X = Piperidino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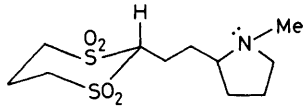
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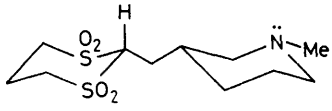
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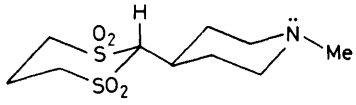
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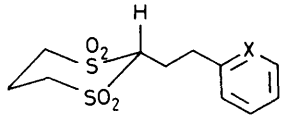
(24) X = CH
(25) X = N

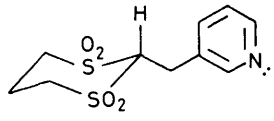
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Table 1. Spectroscopic data for compounds (14), (15), and (17) are recorded in the Experimental section. Most disulphones showed a parent ion in their mass spectra; in their i.r. spectra there were peaks near 1 325 and 1 130 cm^{-1} characteristic of the SO_2 moiety. N.m.r. signals from atoms at the potential H-bonding site are discussed in the next section; other common signals arising from the disulphone ring are (^1H) near δ 3.2 (m) for the 4- and 6-CH_2 groups and near δ 2.4 (m) for the 5-CH_2 group, and (^{13}C) near δ 51.5 and 17.8 p.p.m., respectively, for C-4 and C-6, and for C-5.

Evidence for Intramolecular Interactions.—^1H and ^{13}C N.m.r. data for the disulphone ring methine group, recorded under a variety of conditions, are shown in Table 2. [$^2H_2$]-Dichloromethane was the solvent of choice for detecting intramolecular interactions, being sufficiently polar to dissolve the sulphones but likely to interact only very weakly with the electron donor groups X.* To reduce the possibility of intermolecular association between disulphone molecules, a low (3.2×10^{-2}M) concentration was employed; chemical shifts measured at half this concentration showed no change. Spectra were also recorded at −40 °C to test whether reduced conformational mobility would enhance any interactions.

In contrast, both acetonitrile and pyridine are known to form quite strong intermolecular hydrogen bonds with polar

* Most macroscopic properties used in detecting H-bonds indicate that for interactions involving chloromethanes, $CHCl_3 > CH_2Cl_2$ (ref. 4, p. 45 *et seq.*).

Table 1. Preparative, physical, and analytical data for cyclic disulphones (known compounds indicated with an asterisk)

Compound	Method [a]	Yield (%)	M.p. (°C)	Solvent [b]	Found (%) C	H	N(S)	Formula	Requires (%) C	H	N(S)
(5a)	A	85	185	I	40.1	6.8	(26.4)	$C_8H_{16}O_4S_2$	40.0	6.7	(26.7)
(5b)	A	50	128	I	42.6	7.0		$C_9H_{18}O_4S_2$	42.5	7.1	
(5c)	A	46	138.5	I	44.4	7.35	(23.9)	$C_{10}H_{20}O_4S_2$	44.75	7.5	(23.9)
(6d)	A	40	123.5	I	44.8	7.65	(23.9)	$C_{10}H_{20}O_4S_2$	44.75	7.5	(23.9)
(6e)	A	36	131.5	I	46.5	7.7	(22.7)	$C_{11}H_{22}O_4S_2$	46.8	7.9	(22.7)
(6f)	A	14	129	I	48.9	8.2	(21.8)	$C_{12}H_{24}O_4S_2$	48.6	8.1	(21.9)
(7b)	A	30	179	II	34.5	5.7	(26.4)	$C_7H_{14}O_5S_2$	34.7	5.8	(26.5)
(7c)	A	70	133	II	37.5	6.2	(24.8)	$C_8H_{16}O_5S_2$	37.5	6.3	(25.0)
(7d)	A	69	110	II	40.1	6.6		$C_9H_{18}O_5S_2$	40.0	6.7	
(7e)	A	40	131	II	42.2	6.9	(22.2)	$C_{10}H_{20}O_5S_2$	42.2	7.1	(22.0)
(7f)	A	56	156	II	44.1	7.4	(21.1)	$C_{11}H_{22}O_5S_2$	44.3	7.4	(21.5)
(8b)	A	31	121	II	37.6	6.8	5.4	$C_8H_{17}NO_4S_2$	37.6	6.7	5.5
(8c)	A	30	128	II	39.9	7.0	4.9	$C_9H_{19}NO_4S_2$	40.1	7.1	5.2
(8d)	C	24	86	II	42.1	7.4	4.8	$C_{10}H_{21}NO_4S_2$	42.4	7.5	4.9
(8e)	C	23	121	II	44.0	7.8	4.4	$C_{11}H_{23}NO_4S_2$	44.4	7.8	4.7
(8f)	C	39	117	II	46.0	8.2	4.5	$C_{12}H_{25}NO_4S_2$	46.3	8.1	4.5
(9b)	A	71	108.5	II	42.3	7.6	5.3	$C_{10}H_{21}NO_4S_2$	42.4	7.5	4.9
(9c) [c]	A	52	88	II	43.2	7.8	4.5	$C_{11}H_{23}NO_4S_2$	43.1	7.9	4.6
(10b)	B	38	104	II	42.3	6.9	4.8	$C_{10}H_{19}NO_4S_2$	42.7	6.8	5.0
(10c)	B	46	109	II	44.9	7.2	4.7	$C_{11}H_{21}NO_4S_2$	44.7	7.2	4.7
(11b)	A	67	138.5	II	44.4	7.0	4.8	$C_{11}H_{21}NO_4S_2$	44.7	7.2	4.7
(11c)	A	32	135	II	46.25	7.6	4.2	$C_{12}H_{23}NO_4S_2$	46.55	7.5	4.5
(12b)	A	67	225	IV	40.6	6.5	4.55	$C_{10}H_{19}NO_5S_2$	40.4	6.4	4.7
(12c)	A	32	155.5	IV	42.4	6.6	4.5	$C_{11}H_{21}NO_5S_2$	42.4	6.8	4.5
(13d)	D	78	140	IV	30.4	4.7	(20.5)	$C_8H_{15}BrO_4S_2$	30.1	4.7	(20.1)
(13e)	D	85	141	II	32.8	5.2	(19.0)	$C_9H_{17}BrO_4S_2$	32.45	5.1	(19.2)
(14a) *	A	50	277 [d]	III	34.1	4.9	(30.2)	$C_6H_{10}O_4S_2$	34.3	4.8	(30.5)
(14b)	A	42	211	III	37.6	5.3	(28.2)	$C_7H_{12}O_4S_2$	37.5	5.3	(28.5)
(14c)	A	65	232	III	40.5	5.9	(26.6)	$C_8H_{14}O_4S_2$	40.3	5.9	(26.9)
(14d) *	A	78	200 [e]	III	42.7	6.5	(25.5)	$C_9H_{16}O_4S_2$	42.8	6.4	(25.6)
(17)	B	43	146	II	40.4	7.1	4.9	$C_9H_{19}NO_4S_2$	40.1	7.1	5.2
(18)	B	64	144	II	42.5	7.3	4.8	$C_{10}H_{21}NO_4S_2$	42.4	7.5	4.9
(19)	B	47	204	III	48.7	7.8	4.3	$C_{13}H_{25}NO_4S_2$	48.3	7.8	4.3
(21)	A	39	155	II	44.6	7.5	4.4	$C_{11}H_{21}NO_4S_2$	44.7	7.2	4.7
(24)	A	40	182	II	50.1	5.6		$C_{12}H_{16}O_4S_2$	50.0	5.6	
(25)	A	55	154	IV	45.9	5.6	4.8	$C_{11}H_{15}NO_4S_2$	45.7	5.2	4.8
(26)	A	73	204	IV	42.1	5.0	4.6	$C_{10}H_{13}NO_4S_2$	42.2	4.9	4.9

[a] See Experimental section. [b] I Benzene–light petroleum; II benzene; III MeOH; IV $CHCl_3$–CCl_4 (1 : 1). [c] Crystallises with 0.5 H_2O. [d] With decomp. [lit.,[10] 274 °C (decomp.)]. [e] Lit.,[11] 200—201 °C.

CH groups,[4] and thus might compete with the donor group X if there is an intramolecular interaction. Trifluoroacetic acid on the other hand, would be expected to uncouple any intramolecular interaction by protonating the electron donor group X. ^{13}C Chemical shifts and one-bond CH coupling constants were also recorded for the ring methine group to test the sensitivity of these parameters to the interactions of interest.

Reference Compounds.—Chemical shifts in [$^2H_2$]dichloromethane at 20 °C for reference compounds (5) and (6) all lie in the range δ 4.22 ± 0.04, as do those for methoxy compounds (7d—f) having side-chain lengths n = 4—6, and dimethylamino-compounds (8e) and (8f), having n = 5, 6. For the same compounds in [$^2H_3$]acetonitrile, a range δ 4.52 ± 0.02 is found, and on addition of pyridine (0.25 and 0.75 ml to a more concentrated solution), this becomes, respectively, δ 4.82 ± 0.03 and 5.10 ± 0.05. Clearly there are no significant intramolecular interactions in structures (7d—f) and (8e) and (8f). The above chemical-shift ranges may be used for reference purposes, the small downfield shift in [$^2H_3$]acetonitrile and the large (stepwise) shift on addition of pyridine being consistent with the formation of intermolecularly H-bonded complexes between these solvents and the polar methine.*[,14,15] In all other compounds studied [except (24), *vide infra*] the methine chemical shift in [$^2H_2$]dichloromethane lies to lower field (δ 4.3—6.4); we believe this shift to arise from an intramolecular interaction of the hydrogen-bonding type, involving the donor group X.

The strength of such a hydrogen bond in a given solvent at constant temperature is related to its formation constant, which in turn will depend on the electron-donor properties of X, the conformational mobility of the molecule, and steric factors. The methine ^1H n.m.r. chemical shift will be influenced by the above formation constant, as well as by inductive (I) and anisotropic effects due to the group X. The latter are, however, believed to be small for alkoxy- and dialkylamino-groups.[16]

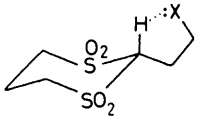
Effect of Chain Length n.—The data in Table 2 show that significant downfield shifts are observed in [$^2H_2$]dichloromethane for methoxy- and amino-compounds having n = 2 or 3. With the exception of amines (11c) and (18), the shift is largest for n = 2. A small contribution from the inductive effect of X is indicated by the signal from the side-chain

* The downfield shift in acetonitrile will be artificially small owing to the nitrile group anisotropy;[14,15] for complex formation constants with *e.g.* chloroform, magnitudes are acetonitrile > pyridine (P. J. Berkeley and M. W. Hanna, *J. Phys. Chem.* 1963, **67**, 846).

Table 2. N.m.r. data (^1H and ^{13}C/p.p.m.) for the potential proton donor site in cyclic disulphones

Compound	Terminal substituent	Chain length (*n*)	δ(^1H) [a] CD_2Cl_2 −40 °C	CD_2Cl_2 20 °C	CD_3CN 20 °C	Pyridine [b] 0.25 ml	Pyridine [b] 0.75 ml	TFAA [c] 0.1 ml	TFAA [c] 0.3 ml	δ(^{13}C) [a] CD_2Cl_2 20 °C	$^1J_{CH}$ (Hz)
(5a)	Pr^i	1	4.33	4.25	4.54					79.05	146.7
(5b)	Pr^i	2	4.26	4.18	4.51	4.79	5.05			80.60	147.5
(5c)	Pr^i	3	4.30	4.22	4.53	4.82	5.10	4.50	4.58	80.80	145.2
(6d)	Et	4	4.29	4.21	4.53	4.82	5.09			80.79	145.7
(6e)	Et	5	4.30	4.21	4.53	4.83	5.10			80.67	147.3
(6f)	Et	6	4.29	4.20	4.53	4.81	5.12			81.02	144.6
(7b)	OMe	2	4.67	4.57	4.75	4.97	5.30			77.17	150.5
(7c)	OMe	3	4.47	4.39	4.61	4.88	5.18	4.65	4.72	80.62	150.2
(7d)	OMe	4	4.31	4.23	4.54	4.85	5.15			80.41	148.9
(7e)	OMe	5	4.31	4.23	4.53	4.82	5.10			80.48	145.2
(7f)	OMe	6	4.29	4.21	4.52	4.82	5.11			80.95	150.5
(8b)	NMe_2	2	4.94	4.86	4.88	5.07 [d]	5.36 [e]	4.86	4.91	77.17	147.3
(8c)	NMe_2	3	4.65	4.62	4.68	4.92 [d]	5.27 [e]	4.60	4.66	80.40	143.8
						4.85 [c]	5.13 [c]				
(8d)	NMe_2	4	4.45	4.33	4.57	4.81 [d]	5.12 [e]			80.83	140.3
(8e)	NMe_2	5	4.41	4.26	4.54	4.78 [d]	5.16 [e]			80.79	142.5
(8f)	NMe_2	6	4.33	4.23	4.53	4.78 [d]	5.16 [e]			80.65	144.6
(9b)	NEt_2	2	4.99	4.86	4.82	5.14	5.45	4.85	4.88	77.62	145.2
(9c)	NEt_2	3	4.88	4.78	4.88					80.75	152.8
(10b)	Pyr [f]	2	4.97	4.88	4.92					77.42	148.0
(10c)	Pyr [f]	3	4.61	4.63	4.65	5.08	5.30	4.64	4.71	80.41	145.2
(11b)	Pip [g]	2	4.97	4.88	4.93	5.25	5.50			77.71	145.7
(11c)	Pip [g]	3	5.08	5.03	4.86	5.24 [c]	5.35 [c]	4.65	4.75 [d]	80.26	145.2
(12b)	Mor [h]	2	4.96	4.84	4.94	5.26	5.56	4.88	4.94	77.43	148.4
(12c)	Mor [h]	3	4.75	4.72	4.76	5.16	5.45	4.67	4.73	80.36	151.6
(17)	NMe_2	2	5.11	5.06	5.05	5.30	5.51	4.85	4.92	77.26	144.1
(18)	NMe_2	3	5.64	5.53	5.07	5.63 [c,d]	5.68 [c,i]	4.65	4.70 [d]	78.12	147.0
(19)	Pip [g]	3	6.77	6.40	5.53	5.95 [c]	5.97 [c]	4.61	4.70	77.96	144.2
(20)	Pip [g]	3	4.83	4.83	4.70	5.01	5.31	4.46	4.69	78.11	144.4
(21)	NPyr [j]	3	4.49	4.46	4.59					81.03	145.4
(24)	Ph	3	4.20	4.16	4.47	4.93	5.20	4.35	4.43	79.57	148.5
(25)	2-Py [k]	3	4.65	4.61	4.66	5.08	5.35	4.70	4.78	79.80	150.6
(26)	3-Py [l]	3	4.55	4.48	4.92					81.57	145.0

[a] Relative to internal Me_4Si; solutions 3.2 × 10^{-2}M unless otherwise indicated. [b] Volume added to 0.25 ml of a 0.5M-CD_3CN solution. [c] Volume of trifluoroacetic acid (TFAA) added to 0.25 ml of a 0.5M-CD_2Cl_2 solution. [d] 0.2 ml Added. [e] 0.8 ml Added. [f] Pyrrolidinyl. [g] Piperidino. [h] Morpholino. [i] 0.6 ml Added. [j] *N*-Methylpyrrolidin-2-yl. [k] Pyridin-2-yl. [l] Pyridin-3-yl.



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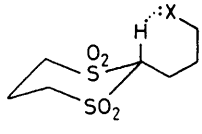


(28)

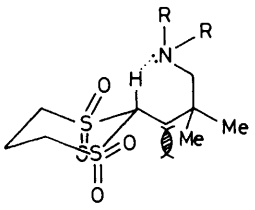
methylene group α to the ring methine: this is near δ 2.5 in (7b) and (8b), but between δ 2.2 and 2.3 in nearly all structures having $n = 3$, and in all compounds (5) and (6). However, the largest contribution must be from direct interaction between X and the methine proton rather than the inductive effect, since the more electronegative methoxy-group shows a smaller shift.

For $n = 2$ and 3, stable five- (27) and six-membered rings (28) are possible; the dimethylamino-compound (8d; $n = 4$), which appears to have a small interaction, could form a seven-membered ring, but shifts are not observed for longer chains, consistent with observations of more common intramolecular hydrogen bonds.

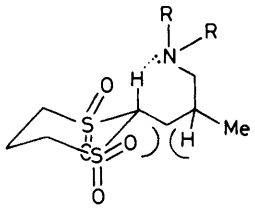
Effect of Donor Group X.—As indicated above, NR_2 groups are more effective donors to CH than is OMe, although a theoretical treatment has suggested that they should be similar.[17] In addition, amino-compounds having $n = 2$ apparently behave differently as a class from those having $n = 3$. When $n = 2$, the methine chemical shift (δ 4.86 ± 0.02) appears to be independent of the nitrogen substituents; when $n = 3$ it ranges from δ 4.62 to 5.03 [compounds (8)—(12)], the order, which does not reflect the group basicity, being NMe_2 ~ pyrrolidinyl < morpholino < NEt_2 < piperidino. Further, the most effective donor, piperidine, is exceptional in showing a larger shift for $n = 3$ (11c) than for $n = 2$ (11b).

The observed methine chemical shift will be a weighted average of contributions from all conformations adopted by a molecule, and will move to lower field as the contribution from the H-bonded form increases. The above results are not easy to rationalise, but factors must include: (*a*) a less favourable nitrogen lone-pair geometry for $n = 2$, balanced by a statistical factor favouring close approach of nitrogen to the methine, relative to the situation for $n = 3$; (*b*) steric interactions between the *N*-substituents and the sulphone oxygen atoms, which will vary with *n*; and (*c*) the rate of nitrogen inversion (or ring pseudorotation). Surprisingly, a similar low-field shift (0.0—0.15 p.p.m.) is observed for all compounds (5)—(12) studied on lowering the temperature to −40 °C, the populations of H-bonding conformations apparently being little affected.

Effect of Side-chain Substitution.—Through steric interactions with the sulphone groups and the *N*-substituents, this



(29)



(30)

will effectively reduce the contributions made by some conformations to the chemical shift, and enhance others. When the H-bonded conformation is hindered, as in structure (29) [compound (20) *], a high-field shift [−0.2 p.p.m. relative to (11c)] is observed; if that conformation is not hindered, as in structure (30) [compounds (18) and (19)], a shift to lower field is expected. In practice, the shifts are 0.91 p.p.m. for the dimethylamino-compound (18) and a remarkable 1.37 p.p.m. for piperidino-compound (19), relative to (8c) and (11c) respectively, again showing piperidine to be the better donor. The latter figure represents a downfield shift of 2.15 p.p.m. relative to model compound (5a) (Figure). It is larger than most recorded shifts for formation of *inter*molecular C–H···N interactions,[4,5b] and thus indicates a very significant *intra*molecular hydrogen bond. Further, compound (19) shows an additional shift of 0.37 p.p.m. on lowering the temperature to −40 °C, a process which in this case apparently enhances the contribution due to conformer (30). Preliminary *X*-ray diffraction studies [18] confirm the intramolecular interaction in compound (18); data are being collected for structure (19). The side-chain methyl group in the dimethylamino-compound (17) also causes a (smaller) shift to lower field relative to the unsubstituted analogue (8b).

In the pyrrolidinyl derivative (21) the ring geometry and steric interactions dictate an unfavourable nitrogen lone-pair angle, which seems to be important; thus an upfield shift (−0.17 p.p.m.) is observed relative to (10c).

Incorporation of part of the side chain and the nitrogen atom into a pyridine ring [compound (25)] imposes different geometric requirements, as well as modifying the donor properties and anisotropy of the group. Nevertheless, the downfield shift (0.45 p.p.m.) relative to reference compound (24) confirms a significant interaction. The δ value for the 3-pyridyl derivative (26) probably results from the closer proximity of the aromatic ring.

Effect of Changing the Medium.—Changes in the methine chemical shift on recording spectra in [$^2H_3$]acetonitrile, or with added pyridine or trifluoroacetic acid are fully consistent with the uncoupling of intramolecular interactions. Their magnitudes reflect the apparent strength, both of the original intramolecular, and of the competing intermolecular, H-bonds. Thus, in [$^2H_3$]acetonitrile, a downfield shift of 0.3 p.p.m. is observed for all reference compounds, decreasing to 0.2 ± 0.02 p.p.m. for methoxy-compounds (7b) and (7c) in which there are only weak interactions. For amino-compounds having $n = 2$ and 3, in which the interaction is moderate, the shift is even smaller (0.01—0.10 p.p.m.), and for structures (20), (11c), (18), and (19) in which increasingly strong interactions are indicated, shifts are, respectively, 0.13, 0.17, 0.46, and 0.87 p.p.m. to *high* field. The pattern is similar on addition of pyridine, except that the larger downfield shift caused by this base relative to [$^2H_3$]acetonitrile results in only the most strongly H-bonded compound (19) showing a nett upfield shift.

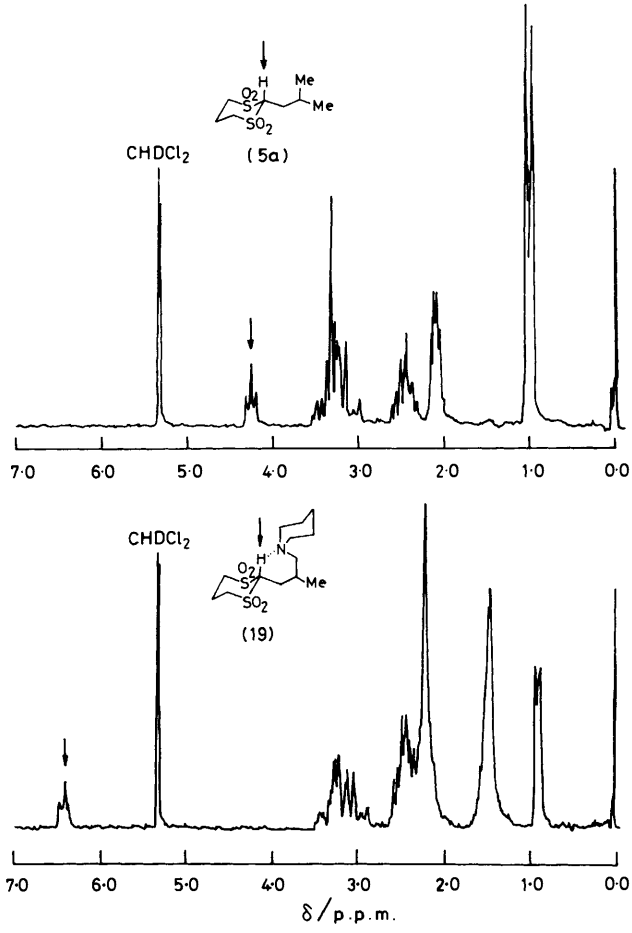


Figure. ^1H N.m.r. spectra of compounds (5a) and (19) in [$^2H_2$]-dichloromethane at 89.6 MHz. The methine signal is arrowed

The change in methine chemical shift on addition of trifluoroacetic acid arises from three factors: the solvent anisotropy [a downfield shift is indicated by (5c)]; the uncoupling of any intramolecular interactions (causing an upfield shift); and the increased −I effect due to protonation of X (causing a downfield shift). The last-named factor is seen to be greater for $n = 2$ than for $n = 3$ as would be expected. Approximately constant values for all amino-compounds having $n = 3$ (and for those with $n = 2$) suggest that intramolecular interactions are almost entirely uncoupled. Again it is the same four compounds which show a nett upfield shift (with 0.1 mol acid) and in the same order: (20) < (11c) < (18) < (19). The signal moves to lower field once more on further addition of acid, the increased concentration of $\overset{+}{N}HR_2$ resulting in a larger −I effect.

Effect on Other N.M.R. Parameters.—The ^{13}C signal for chloroform has been shown to be solvent-sensitive, moving increasingly to lower field (by up to 4.2 p.p.m.) with increasing donor properties of the solvent, as a result of intermolecular H-bond formation.[15] Likewise, $^1J_{CH}$ increased (by up to 9 Hz) in approximately the same order, possibly owing to an increase in the CH bond s-character arising from electronic repulsion by the donor electrons on the basic solvent.[19]

In Table 2, δ (^{13}C) is seen superficially to range over 4.4

* In the crystal, this molecule is in an extended conformation with no intramolecular interaction.[1]

p.p.m., and $^1J_{CH}$ over 12.5 Hz; while the latter shows no apparent correlation with structure, some trends can be seen with δ (^{13}C). For all compounds (5)—(12) having $n > 2$, values lie in the narrow range δ 80.26—81.02, thus indicating little sensitivity either to the donor group X or to the ring size. This is also apparent on comparing compounds (24) and (25). Likewise for $n = 2$, values range only from δ 77.17—77.71, the exception being compound (5b); apparently the upfield shift is somehow related to the presence of non-bonding electrons on the donor group X. In the case of (5a), however, it arises from the γ-effect of the side-chain methyl groups. Compounds (18)—(20) also show a shift to high field, and although this might be accommodated by the γ-effect due to two methyl groups in (20), it is too large to be due to the one methyl group in structures (18) and (19), and apparently in the wrong direction to be due to H-bonding. In the latter two compounds, and possibly also in those having $n = 2$, the anomalous shifts may arise from reduced conformational mobility. It is well known that small structural changes cause significant changes in δ (^{13}C); these changes may well be larger than shifts due to C–H · · · X interactions.

Coupling ($^3J_{HH}$) between the disulphone ring methine proton and the side-chain α-CH_2 group should give rise to a symmetrical triplet signal for the former, except when the methylene group is rendered diastereoisotopic by side-chain substitution. In practice, in [$^2H_2$]dichloromethane, the signal is more complex for most methoxy- and amino-compounds, showing evidence of two coupling constants (4.6—7.0 Hz), and thus of restricted conformational mobility. Further, quite large changes in the methine signal line-shape (and elsewhere in the spectrum) occur on lowering the temperature to −40 °C. In contrast, the signal in [$^2H_3$]acetonitrile is a symmetrical triplet (*J* 5.9 Hz), and no significant changes are observed in the spectra on lowering the temperature, suggesting free rotation of the side chain and absence of intramolecular interactions.

Experimental

I.r. spectra were recorded in Nujol on a Perkin-Elmer 577 spectrophotometer; ^{1}H (89.56 MHz; ±0.2 Hz) and ^{13}C (22.5 MHz; ±1.2 Hz) n.m.r. spectra on a JEOL FX 90Q instrument, using Me_4Si as internal reference; and mass spectra on a Hitachi RMS-4 spectrometer.

1,3-Dithian 1,1,3,3-tetraoxide (3) was prepared (89%) as reported by Posner and Brunell; [20] most halides (4) were available commercially, but of those which were not (4; X = MeO; Y = Br) were prepared either from the methoxy-alcohol with PBr_3,[21] or from the dibromide with NaOMe–MeOH.[22] 3-Bromo-1-chloro-2-methylpropane [for compounds (18) and (19)] was prepared from 3-chloro-2-methylpropene.[23]

Preparation of Mono-substituted Disulphones.—Method A. (*a*) Compounds (5)—(7), (13f), and (24). A solution of the disulphone (3) (0.92 g, 0.005 mol) in dry *N*,*N*-dimethylformamide (DMF) (30 ml) was treated with methanolic NaOMe (5.5 ml; 1M). After 10 min, the appropriate halide (4) (0.005 mol) was added dropwise with stirring, the mixture was heated on an oil-bath (70—80 °C) for 3 h, water (5 ml) was added, and the solvent was removed under reduced pressure. The residue was extracted with $CHCl_3$, the extract was filtered, dried ($MgSO_4$), and evaporated, and the residue was recrystallised (see Table 1).

(*b*) Amino-compounds. As in (*a*) above; only the halogeno-amine hydrochloride (0.0055 mol) was dissolved in methanolic NaOMe (6 ml; 1M), and the mixture added to the DMF solution of the sodium salt of (3).

Method B. Sodium hydride (50% dispersion; 0.26 g, 0.0054 mol) was added to a solution of the disulphone (3) (0.92 g, 0.005 mol) in dry DMF (30 ml), and the mixture heated to 70—80 °C until evolution of H_2 ceased. A solution containing the appropriate halogeno-amine (4) (0.005 mol) [prepared from the HCl salt in dry DMF (10 ml) by reaction with sodium hydride (0.005 mol)] was added, and the mixture was stirred at 80 °C for 3 h. Water (5 ml) was added, the solvent was removed under reduced pressure, and the product isolated as for method A. 2-(2-*Dimethylaminopropyl*)-1,3-*dithian* 1,1,3,3-*tetraoxide* (17) had δ (^{1}H) (CD_2Cl_2) 5.06 (1 H, dd, *J* 6.2, 4.0 Hz), 3.24 (4 H, m), 3.06 (1 H, m), 2.44 (2 H, m), 2.16 (6 H, s; and 2 H, m), and 0.96 (3 H, d, *J* 7.0 Hz); δ (^{13}C) (CD_2Cl_2) 77.26 (ring C-2), 56.7 (side-chain CH), 51.73 and 51.32 (ring C-4 and C-6; diastereoisotopic), 39.55 (NMe), 24.57 (side-chain CH_2), 17.97 (ring C-5), and 11.14 p.p.m. (side-chain Me); analytical and physical data in Table 1.

Method C. A solution of the appropriate halogeno-sulphone (13) (0.005 mol) in methanolic dimethylamine (30 ml; 33%) was heated under reflux, using a Me_2CO–solid CO_2 condenser, for 3 h. The solvent was evaporated, the residue was dissolved in 2M-HCl (30 ml) and the solution extracted with $CHCl_3$ (3 × 20 ml). The aqueous layer was basified with solid $NaHCO_3$, extracted with $CHCl_3$ (2 × 20 ml), the extract was dried and evaporated, and the residue was recrystallised. Use of methanolic pyrrolidine or piperidine in place of dimethylamine led to the spiro-products (14).

Method D. The appropriate methoxy-compound (7) (0.005 mol) was refluxed in concentrated HBr (20 ml) for 3 h. The mixture was cooled, diluted with water (200 ml), and extracted with $CHCl_3$ (2 × 20 ml). The extracts were dried and evaporated, and the residue recrystallised.

Preparation of the Spiro-disulphones (14).—Reaction of the dihalides (4; X,Y = Br or Cl; $n = 2$—5) with the disulphone (3) by method A gave 1,3-dithian-2-spirocyclopropane 1,1,3,3-tetraoxide (14a), $M^{+\cdot}$ 210; δ (^{1}H) 3.37 (4 H, t, *J* 6 Hz, CH_2SO_2), 2.51 (2 H, m, 5-CH_2), and 1.78 (4 H, s, cyclopropane CH_2); δ (^{13}C) 51.62 (sulphone C-4 and -6), 51.47 (sulphone C-2), 18.96 (sulphone C-5), and 12.42 p.p.m. (cyclopropane C-2 and -3); 1,3-*dithian*-2-*spirocyclobutane* 1,1,3,3-*tetraoxide* (14b), $M^{+\cdot}$ 224; δ (^{1}H) 3.28 (4 H, m, CH_2SO_2), 2.82 (4 H, m, cyclobutane CH_2), and 2.31 (4 H, m, 5-CH_2 and cyclobutane CH_2); δ (^{13}C) [$(CD_3)_2SO$] 79.04 (sulphone C-2), 46.16 (sulphone C-4 and -6), 23.08 (cyclobutane C-2 and -4), 17.06 (sulphone C-5), and 15.22 p.p.m. (cyclobutane C-3); 1,3-*dithian*-2-*spirocyclopentane* 1,1,3,3-*tetraoxide* (14c); $M^{+\cdot}$ 238; δ (^{1}H) 3.39 (4 H, t, *J* 6 Hz, CH_2SO_2), 2.4 (6 H, m, 5-CH_2 and cyclopentane CH_2), and 1.9 (4 H, m, cyclopentane CH_2); and 1,3-dithian-2-spirocyclohexane 1,1,3,3-tetraoxide (14d), $M^{+\cdot}$ 252; δ (^{1}H) 3.30 (4 H, t, *J* 6 Hz, CH_2SO_2), 2.3 (3 H, m, 5-CH_2), 2.13 (4 H, m, cyclohexane CH_2), and 2.0—1.5 (6 H, m, cyclohexane CH_2).

Preparation of Disulphone (15) *by the Mannich Reaction.*—To a mixture of the disulphone (3) (3.69 g, 0.02 mol) and methanolic Me_2NH (3.3 ml; 33%) at 20 °C was added dropwise aqueous CH_2O (2 ml; 40%). The solution was kept at 35—40 °C for 3 h, raised to 80 °C for 1 h, and evaporated under reduced pressure. The residue was extracted with 2M-NaOH (30 ml), and the extract filtered and acidified with 2M-HCl to precipitate the 2,2′-methylenebis(1,3-dithian 1,1,3,3-tetraoxide) (15) (65%), m.p. 340 °C (decomp.) (lit.,[12] >300 °C); $M^{+\cdot}$ −183; δ (^{1}H) [$(CD_3)_2SO$] 5.35 (2 H, t, *J* 6.5 Hz, 2-CH), 3.68 (8 H, m, CH_2SO_2), 2.80 (2 H, d, *J* 6.5 Hz, bridge CH_2), and 2.4 (4 H, m, 5-CH_2). The same product was obtained when the ratio of reactants, the temperature, and the heating time were varied within wide limits.

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