Assignment of Sulphoxide Configuration by the Nuclear Magnetic Resonance Method

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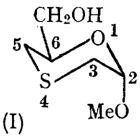
THE significant deshielding[1,2] of protons that are *syn*-axial to an *ax*-sulphoxide group in appropriately substituted derivatives [*e.g.* compounds (I_{ax})—(IV_{ax})] of 1,4-oxathian *S*-oxide can be used[2] for assigning absolute configuration at the S → O centre. However, the usefulness of the method may be limited by uncertainty concerning the conformation adopted in solution by these potentially flexible molecules. It is possible to use,[2] in such assignments, chemical-shift data for all of the protons in the immediate environment of the sulphoxide group. For thian 1-oxide, the chemical shift difference (δ) for the protons of the methylene groups that are vicinal to the sulphoxide centre is larger (0·87 p.p.m.) when the lone pair of electrons on sulphur is axial than when it is equatorial[3] (0·48 p.p.m.). Also, the geminal coupling for these protons is smaller when the lone pair of electrons is axial than when it is equatorial,[4] and also smaller than for the parent sulphide.

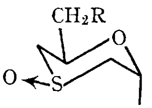
We report first-order 100 MHz n.m.r. analyses of a series of 2,6-disubstituted 1,4-oxathian derivatives [(I)—(IV)] and their *S*-oxides. These analyses show a clear pattern of chemical shift and coupling-constant differences that are related to the chirality of the sulphoxide group and provide a more reliable basis for configurational assignment.

The n.m.r. data for the 1,4-oxathian derivatives are listed in the Table. The steric requirements[5] for the observed vicinal coupling constants are satisfied only if the 1,4-oxathian derivatives are essentially in the near-ideal chair conformations depicted (I)—(IV). The large (*ca.* 2 Hz) long-range coupling constants $J_{3eq,\,5eq}$ which involve the bond sequence H–C–S–C–H also indicate chair conformations, being closely similar in magnitude to those observed for H–C–C–C–H and H–C–O–C–H systems and for which the preferred pathway has been postulated[6] to involve a "planar M" arrangement of the bonds. Long range ($J_{3eq,\,5eq}$) couplings were observed for all of the compounds listed in the Table, but, in some cases, accurate data could not be obtained.

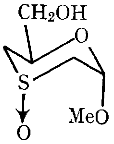
The essential conformational homogeneity of the 1,4-oxathian derivatives listed in the Table permits an assessment to be made of the usefulness, in assigning configuration to sulphoxides, of the n.m.r. data for the protons of the methylene groups that are vicinal to the sulphoxide groups. Comparison of the data for the *eq*-sulphoxides [(I*eq*)—(IV*eq*); although more values were available for compound (I*eq*; R = H) than for (I*eq*; R = OH), there were no major differences in the spectra] and the *ax*-isomers (I*ax*)—(IV*ax*) reveals that, in the former group, the chemical shift differences $\delta_{3ax,\,3eq}$ and $\delta_{5ax,\,5eq}$ are in the ranges 0·69—0·94 and 0·78—0·95 p.p.m. In the latter group, the ranges were 0·48—0·68 ($\delta_{3ax,\,3eq}$) and 0·28—0·57 p.p.m. ($\delta_{5ax,\,5eq}$). By analogy with thian 1-oxide,[3] compounds in the latter group may thus be assigned a configuration having the lone pair of electrons and the S → O bond equatorial and axial, respectively. In support[4] of this configurational assignment is the fact that the geminal coupling-constants (11·3—12·8 Hz) for the *eq*-sulphoxides are smaller than those (13·8—15·5 Hz) for the respective *ax*-sulphoxides.



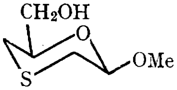
(I)



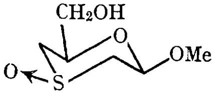
(I*eq*)



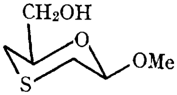
(I*ax*)



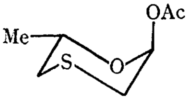
(II)



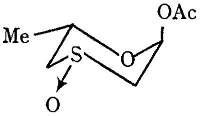
(II*eq*)



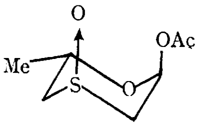
(II*ax*)



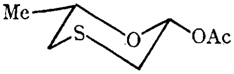
(III)



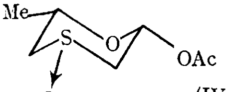
(III*eq*)



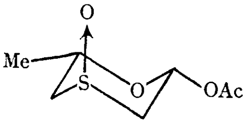
(III*ax*)



(IV)



(IV*eq*)



(IV*ax*)

The above assignment of sulphoxide configuration accords with that based[1,2] on the "*syn*-axial effect", in which the significant deshielding of H(6*ax*) in the *ax*-sulphoxides, and of H(2*ax*) in compounds (II*ax*) and (IV*ax*), is attributed to an *ax*-S → O bond. The configuration and conformation assigned to compound (I*eq*) on the basis of the above n.m.r. data accords with that unequivocally established by *X*-ray[7] and chemical methods.[8] A firm foundation is thereby provided for the general applicability of the n.m.r. method as a useful and convenient additional means of assigning absolute configuration to appropriate pairs of stereoisomeric sulphoxides.

The magnitude of the chemical-shift differences for the H(6*ax*) protons in compounds (I*eq*) and

N.m.r. data[a] *for some 2,6-disubstituted derivatives* (I)–(IV) *of* 1,4-*oxathian and the derived axial* (I_{ax})–(IV_{ax}) *and equatorial sulphoxides* (I_{eq})–(IV_{eq})[f].

	H(2*eq*)	H(2*ax*)	H(3*eq*)	H(3*ax*)	H(5*eq*)	H(5*ax*)	H(6*ax*)	J_{2eq3ax}	J_{2eq3eq}	J_{2ax3ax}	J_{2ax3eq}	J_{3ax3eq}	J_{3eq5eq}	J_{5ax6ax}	J_{5ax5eq}	J_{5eq6ax}
(I)[10]	5·18	—	7·57	7·02	7·72	7·28	5·75	2·9	1·8	—	—	13·8	1·8	10·9	13·8	[e]
(I*eq*)[8,b]	4·88	—	6·2–6·9	7·32	6·2–6·9	7·32	6·07	2·8	2·0	—	—	12·2		11·1	12·3	
	(4·94)		(6·43)	(7·37)	(6·48)	(7·47)	(5·94)	(2·9)	(∼2·0)			(12·1)	(2·9)	(11·8)	(12·0)	[e]
(I*ax*)[8]	4·97	—	6·75	7·43	[e]	[e]	5·25	4·0	—	—	—	14·8	[e]	[e]	[e]	[e]
(II)[9]	—	5·40	7·45	7·35	7·77	7·43	6·10	—	—	8·1	2·9	13·0	[e]	10·5	13·8	[e]
(II*eq*)[9]	—	5·52	[e]	7·37	6·61	7·39	(6·27)	—	—	10·0	1·6	11·8	[e]	10·8	12·8	[e]
(II*ax*)[9]	—	4·92	7·03	7·52	7·16	7·44	5·57	—	—	9·4	1·5	14·2	2·6	11·1	14·2	1·7
(III)[c]	3·86	—	7·66	6·97	7·51	7·37	5·75	2·8	—	—	—	14·2	[e]	10·0	13·0	[e]
(III*eq*)[c]	3·58	—	6·57	7·26	6·45	7·40	5·85	2·8	∼2	—	—	12·8	[e]	11·1	12·2	[e]
(III*ax*)[c]	3·67	—	6·83	7·35	7·07	7·42	5·02	3·5	1·7	—	—	15·5	2·5	10·3	15·0	[e]
(IV)[10]	—	4·17	7·55	7·31	7·80	7·52	5·98	—	—	9·0	2·7	13·1	1·2	9·9	13·5	1·9
(IV*eq*)[d]	—	4·26	6·40	7·30	6·59	7·47	6·20	—	—	10·1	1·6	11·3	1·8	11·5	12·0	1·8
(IV*ax*)[1]	—	3·52	6·93	7·47	7·05	7·62	5·20	—	—	9·8	1·9	14·2	2·2	10·8	13·8	1·9

[a] N.m.r. spectra were obtained at 100 MHz with a JEOL, JNM-4H-100 spectrometer for 5% solutions in $CDCl_3$ with Me_4Si as internal reference. Chemical shifts are given on the τ scale and J values in Hz.

[b] Data given are for formula (I*eq*; R = OH), and the values in parentheses are for compound (I*eq*; R = H). The latter compound (b.p. 96—98°/0·1 mm., $[\alpha]_D^{25}$ +97°) was obtained[11] by reduction with Raney nickel of the 6-iodo-derivative {(I*eq*; R = I), m.p. 113—114°, $[\alpha]_D^{25}$ +59°} formed by the action of sodium iodide–acetone on the 6-methanesulphonate[8] (I*eq*; R = $O{\cdot}SO_2Me$).

[c] Compound (III) {b.p. 80—90°/0·1 mm., $[\alpha]_D^{27}$ *ca.* 0° (EtOH)} was obtained by equilibration of anomer (IV)[10] with toluene-*p*-sulphonic acid in acetic acid–acetic anhydride (1:1). With periodate, compound (III) gave the *eq-S*-oxide {(III*eq*), m.p. 77—78°, $[\alpha]_D^{32}$ −90° (EtOH)}. Equilibration of sulphoxide (IV*ax*) with the above reagent gave a mixture of products (equilibration at both sulphoxide and anomeric centres) from which the *ax*-sulphoxide {(III*ax*), oil, $[\alpha]_D^{27}$ −15° (EtOH)} was isolated by chromatography on silica gel.

[d] M.p. 92—93°, $[\alpha]_D^{23}$ +8°, isolated by chromatography on silica gel of the mixture reported in ref. 1.

[e] Because of superposition, accurate values were not obtainable.

[f] For comparison, the numbering shown in formula (I) is used for all the 1,4-oxathian derivatives. Thus, the anomeric proton is H(2) in each case, whereas strict nomenclature would make it variously H(2) or H(6) depending on alphabetization of substituents.

(I*ax*) was previously attributed[1] to deshielding of H(6*ax*) in isomer (I*ax*) by the S → O group, and was rationalised in terms of a *syn*-axial proximity effect and/or acetylenic-type anisotropy of the S → O bond. The results reported here suggest that this is an over-simplification. In each of the four series (Table), the signals for the H(6*ax*) protons in the equatorial (*eq*) sulphoxides are at higher field (0·10—0·32 p.p.m.) than those for the respective parent oxathians, whereas the H(6*ax*) signals for the axial (*ax*) sulphoxides occur at lower field (0·50—0·78 p.p.m.) than for the oxathians. A similar situation obtains for the H(2*ax*) signals of the compounds in series (II) and (IV). The shielding effect in the *eq*-sulphoxides is relatively small (0·09—0·32 p.p.m.), but, for the analogous situation in the pairs of sulphoxides of derivatives of methyl 2,6-anhydro-2-thio-α-D-altropyranoside,[2] the shielding effect is larger than the deshielding effect. This may be due to the near-boat conformation of the 1,4-oxathian ring in these compounds. However, the utility of the "*syn*-axial effect" in configurational assignment of sulphoxides is not adversely affected by these observations, since the magnitude of the chemical-shift differences for the various pairs of diastereoisomeric sulphoxides is of the same order (0·6—1·0 p.p.m.). Any chemical-shift differences attributed to the sulphoxide group should be rationalised in terms of its total electron distribution and not simply in terms of the deshielding effect of an axially oriented S → O bond.

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