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CONFIGURATIONAL CORRELATIONS FOR CHIRAL EPISULPHIDES AND EPISULPHOXIDES BY ^{1}H NMR SPECTROSCOPY IN OPTICALLY ACTIVE SOLVENT

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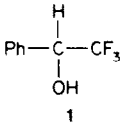
Abstract—Optically active 2,2,2-trifluorophenylethanol, when used as NMR solvent, causes enantiomeric spectral dissimilarities for chiral episulphides and episulphoxides; the relative field positions of non-equivalent NMR resonances are analysed with respect to the absolute configuration of the solvated compounds.

The problem of the direct determination of enantiomeric purity can be successfully solved by ^{1}H NMR procedures based on diastereoisomeric interactions between enantiomeric solutes and optically active solvents[1] or chiral lanthanide shift reagents.[2] Chiral solvents or shift reagents that render enantiotopic groups diastereotopic and anisochronous can also be used in absolute configuration correlations of partially resolved compounds. Studies of this type can be undertaken if a closely related series of optically active substrates of known absolute configuration is available. Moreover, these ^{1}H NMR procedures become extremely important if they can be applied to neutral or unstable compounds. In a previous study we pointed out that the use of the chiral solvent **1** causes the NMR spectra of the enantiomers of a number of simple epoxides to be non-identical, and that this spectral non-equivalence allows an empirical assignment of the absolute configuration.[3]

In order to ascertain the influence of the hetero-atom of the 3-membered ring on the magnitude and on the sense of the enantiomeric spectral non-equivalences,[4] and also to test the behaviour of more dissymmetric cyclic systems, we used the same chiral solvent, namely the (*R*)-(−) 2,2,2-trifluorophenylethanol **1**, to study configurational correlations for the more representative simple, racemic and optically active episulphides and episulphoxides of type **2** and **3**, respectively.



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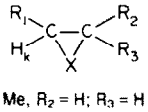
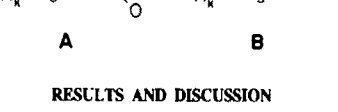


	X = S	X = SO
R_1 = Me, R_2 = H; R_3 = H	**(2,a)**	**(3,a)**
R_1 = Bu^t, R_2 = H; R_3 = H	**(2,b)**	**(3,b)**
R_1 = Ph; R_2 = H, R_3 = H	**(2,c)**	**(3,c)**
R_1 = Ph, R_2 = H, R_3 = Ph	**(2,d)**	**(3,d)**
R_1 = Ph, R_2 = Ph, R_3 = H	**(2,e)**	
R_1 = Me, R_2 = H, R_3 = Me	**(2,f)**	

Synthesis and configuration assignment of episulphides and episulphoxides

Episulphides **(2,a)**–**(2,e)** were synthesised from the corresponding racemic and optically active oxiranes of known absolute configuration and optical purity, by reaction with potassium thiocyanate or with thiourea.[5] Optically active *trans*-2, 3-butylene episulphide **(2,f)** was obtained from the corresponding cyclic carbonate, starting from (*R,R*)-(−)-2,3-butandiol.[6] The absolute configurations of the chiral episulphides reported in Table 1 are assigned in cognizance of the fact that the reaction of the oxirane ring with thiocyanate or thiourea, or the reaction of thiocyanate salts with cyclic carbonates of 1,2-diols, are known to occur with inversion of configuration at both of the carbon atoms of the ring.[5]

Racemic and optically active episulphoxides were obtained by oxidation at −30° of the corresponding episulphides with peroxybenzoic acid in CH_2Cl_2, as described by Kondo and Negishi.[7] These authors found that the oxidations of episulphide compounds with peroxyacids proceed with an extremely high degree of stereoselectivity, giving the exclusive formation of the *anti*-isomer of type **A**. The results of our syntheses, as well as our NMR studies, which were carried out in order to analyse the anisotropy effect of the suphinyl function of compounds **3** with respect to the simple episulphides **2**,[8] are in good agreement with those of the Japanese authors.[7] Therefore, following their configurational assignment, i.e. the *anti*-structure **A** for the episulphoxides obtained **3**, we also conclude that, starting from optically active episulphides of (*S*) absolute chirality at the asymmetric C atom, the absolute configuration of the chiral S atom of the optically active forms of the compounds **(3,a)**–**(3,c)** is (*S*).†



A **B**

RESULTS AND DISCUSSION

The enantiomeric chemical-shift differences and the correlation of the ^{1}H NMR relative field position with the absolute configuration of the episulphides **2** and episulphoxides **3** are reported in Table 1. A doubling of the enantiotopic H_k or R_1, R_2, R_3 proton resonances of the compounds **2** and **3** is observed, with the single exception of the *trans*-stilbene episulphide **(2,c)**.

The most essential general point to emerge from the

†It should be noted that in the structure of the *trans*-diphenyl episulphoxide **(3, d)** the S atom is not asymmetric, being linked to two C atoms of the same (*S*) configuration.

Table 1. Enantiomeric chemical-shift differences and correlation of ^{1}H NMR relative field position with absolute configuration for type 2 and 3 compounds in (R)-(−) 1 solution

	Compounds				Δ δ, Hz[a]				Absolute Config.	Field position relative to the reported absolute configuration			
	R_1	R_2	R_3	X	H_k	R_1	R_2	R_3		H_k	R_1	R_2	R_3
(2,a)	Me	H	H	S	0.9	0.0	0.0	0.55	(−)(S)	low	-	-	high
(3,a)	"	"	"	SO	0.87	0.54	0.19	0.47	(+)(1S,2S)	low	high	high	high
(2,b)	Bu^t	H	H	S	1.22	0.25	0.0	0.73	(−)(S)	low	low	-	high
(3,b)	"	"	"	SO	1.53	0.6	0.16	0.8	(+)(1S,2S)	low	low	low	high
(2,c)	Ph	H	H	S	0.85	-[b]	0.0	0.57	(+)(S)	low	-[b]	-	high
(3,c)	"	"	"	SO	2.14	-[b]	1.64	0.68	(+)(1S,2S)	low	-[b]	low	low
(2,d)	Ph	H	Ph	S	0.0	-[b]	0.0	-[b]	(−)(S,S)	-	-[b]	-	-[b]
(3,d)	"	"	"	SO	0.0	-[b]	1.04	-[b]	(−)(2S,3S)	-	-[b]	low	-[b]
(2,e)	Ph	Ph	H	S	0.0	-[b]	-[b]	0.0	———	-	-[b]	-[b]	-
(2,f)	Me	H	Me	S	0.6	0.8	0.6	0.0	(−)(S,S)	low	-	low	-

a) ^{1}H NMR spectra were measured on a JEOL-C60-HL spectrometer at 25 °C using samples composed of 2:1:ca. 3 Mol. ratios of alcohol:compound:CCl_4, respectively. NMR best parameters were calculated by means of an iterative LAOCN 3 program.[16] b) Not determined.

results reported in Table 1 seems to be that the relative field position of the resonances of the proton H_k is correlated to the absolute configuration of the asymmetric C atoms of the 3-membered rings of the episulphides or episulphoxides in a manner which is exactly the same as that observed for the chiral epoxides having the same structure and the same absolute chirality;[3] i.e. in (−) **1** the resonances of the proton H_k of the enantiomers with the (*S*) absolute configuration at the carbon directly linked to the substituent R_1 occur at lower field (low field position) than the corresponding signals of the enantiomers with the (*R*) absolute configuration at the same C atom.

For the episulphides **2** this correlation seems to be confirmed by the field positions of the R_3 proton, which are high for the (*S*) configuration, as also observed for the corresponding epoxides.[3] From the Table 1 we can see that, for the episulphides, the values of Δδ reported are generally lower than the corresponding values obtained for the epoxides. They generally do not allow a convenient direct assessment of the enantiomeric *S*:*R* ratio. Surprisingly, this trend, which seems to be in agreement with the fact that cyclic sulphides are weaker donors than cyclic ethers,[9] is not followed by the simplest dissymmetric episulphide, namely the propylene sulphide (**2,a**). In fact, the chemical shift differences observed for the protons H_k and R_3 of the compound (**2,a**) are higher than the corresponding Δδ values of the propylene oxide,[3] i.e.: Δδ 0.9 (H_k) and 0.55 (R_3) for the compound (**2, a**); 0.47 and 0.0 for the H_k and R_3 protons of the simple propylene oxide, respectively.[3] On the other hand, the result obtained for the *trans*-diphenyl episulphide (**2,d**), i.e. Δδ = 0.0 for the resonances of the proton H_k, seems to be in agreement with the corresponding value obtained in the case of the *trans*-diphenyl epoxide, which is lower than the values of the other epoxides examined.[3] For the enantiomeric *trans*-diphenyl episulphides here considered, spectral dissimilarities are not observed even in experiments carried out in benzene solution or in CCl_4 solution in which a 10-fold excess of the chiral alcohol was used.

This trend can probably be rationalized by the same hypothesis as that recently reported in the literature,[10] that is by taking into account that in cyclic systems the *trans*-disubstituted molecules offer more highly hindered faces to the approach of the chiral solvent than do the monosubstituted compounds or the isomeric *cis*-disubstituted forms. The *trans*-disubstituted cyclic (+) or (−) diastereomers will consequently show lower shifts with chiral solvents of lanthanide reagents than do the monosubstituted compounds or the *meso* diastereomers.

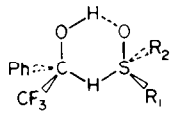
The results reported in Table 1 for the *cis*-1,2-diphenyl episulphide (**2,e**) and the partially resolved form of the (*S,S*)-(−) *trans*-1,2-dimethyl episulphide (**2,f**), both in CCl_4 and (−) **1** solution show that we did not find any significant shift difference between the diastereotopic protons of the *cis*-(**2,e**) derivative, while enantiomeric spectral dissimilarities are still observed (Δδ = 0.6) in the spectra of the chiral *trans*-dimethyl episulphide (**2,f**). These results therefore seem to indicate that, besides the steric effects, other factors, such as, very small solvent solute interaction energies (probably due to a low basic character of the S atom in the aromatic episulphides), are operative in the systems here considered.

The values of the enantiomeric chemical-shift differences obtained for the episulphoxides are generally higher than the corresponding values obtained for the episulphides and follow the order of magnitude reported for other sulphoxides.[11] The ^{1}H NMR spectra of the optically active episulphoxides reported in Table 1, when recorded in (−) **1** solution, do not reveal significant amounts of the corresponding enantiomeric species.

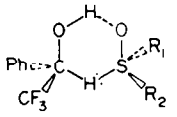
An examination of the magnitudes of non-equivalences reported in Table 1 for the proton H_k shows that the chemical-shift differences depend not only on the structure of the episulphoxides but also on the steric and anisotropic character of the substituents directly linked to

the ring. Thus the enantiotopic H_k protons are not revealed in the *trans*-derivative (**3,d**) and, for the monosubstituted compounds, the dependence from the substituents follows the order Me < Bu^t < Ph.

The results of the ^{1}H NMR relative field positions seem more difficult to analyse. Very recently, Pirkle *et al.*, proposed a solvation model for the problem of assignment of absolute configuration of sulphoxides by NMR.[12] This model is consistent with the fact that partially resolved methyl alkyl and methyl aryl sulphoxides, when examined in the chiral alcohol **1**, show opposite senses of non-equivalence of the two groups on either side of the sulphur and the same senses of nonequivalence for all protons within a given group.[11] This observed NMR behaviour was considered as due to differential shielding of enantiomeric protons by the aromatic ring of the fluoro alcohol **1** in diastereoisomeric solvates **C** and **D** in which the primary interaction is a H–bond from the acidic OH of the alcohol to the basic sulphinyl oxygen, while the secondary stabilizing force consists of the dipolar attraction of the electron-poor carbinyl proton to the electron pair on sulphur.[12] The same model was subsequently applied to analyse the NMR results of cyclic chiral sulphoxides in the optically active solvent **1**[13] and, more recently, to account for the origin and sense of spectral non-equivalence of chiral cyclic and acyclic sulfinate esters.[14]



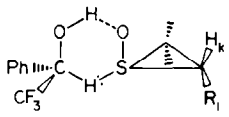
C



D

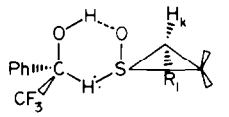
Table 1 reveals that the NMR spectra of the episulphoxides **3** recorded in (−) **1** do not exhibit in a regular manner either the expected contrasting senses of nonequivalence between the substituents situated on either side of the sulphoxide group, namely the H_k and R_1 groups on one side and R_2 and R_3 on the other, or the same trend for all protons within a given group. The lack of regularity is more evident if one examines the results corresponding to the field position of the methylene protons R_2 and R_3 of the monosubstituted episulphoxides (**3, a**)–(**3, c**) relative to the same (*S, S*) configuration. Thus, while for the methyl derivative (**3, a**) these field positions are *high, high*, for R_2 and R_3 respectively, in the case of the t-butyl derivative (**3, b**) they become *low, high*, and in that of the phenyl compound (**3,c**) *low, low*.

Nevertheless, in our opinion, these results do not necessarily mean that the model of Pirkle does not work at all for the sulphoxide systems here considered. In fact, if for our systems we use the model as depicted in the stereoformulae **E** and **F** we can see that the magnetic behaviour of the proton H_k follows the trend expected, i.e. because of shielding by the phenyl of the chiral alcohol we can expect the H_k resonance to occur at lower field for the (*R*)–(*S, S*) solvate than for the (*R*)–(*R, R*) solvate. In these cases the results relative to the resonances of the other R_1, R_2, R_3 protons of the episulphoxides could be explained by the fact that the structure of the 3-membered ring compounds obliges the groups on either side of the sulphur to be much closer and more rigid than they are in other cyclic systems or in open-chain compounds; thus by virtue of their own steric or anisotropic character, they influence each other much more than does the phenyl group of the chiral solvent.



E

(*R*)-(*S,S*) solvate

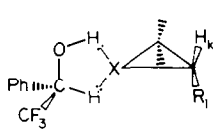


F

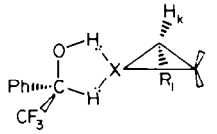
(*R*)-(*R,R*) solvate

If we want to take into account this kind of reasoning, we can also assume that the consistency of the magnetic trend of the H_k proton of the dissymmetric compounds studied by us in the presence of the chiral alcohol **1** (see Table 1 and Ref. 3), might lead one to postulate that the same models **E** and **F** can be applied to problems of configurational assignment of chiral epoxides and episulphides regardless of whether they are a general accurate description of the real conformational states responsible for the magnetic nonequivalences.

In these cases we have to assume that an association between the acidic alcohol function and the basic site of the oxygen in the epoxides, or of the sulphur in the episulphides, *cis* to the H_k proton, is responsible for the formation of the diastereoisomeric solvated species, while secondary attractive forces, which lead to diasteroisomeric short-lived solvates of type **G** and **H**, may occur from the interaction of the carbinyl proton of the fluoro alcohol and the other basic site of the O or S atoms.



G



H

X = O, S.

The models **E–H**, besides the secondary interactions due to the acidic character of the carbinyl hydrogen of **1** and to weakly basic sites of the solutes, do not take into account other factors such as attractive interactions between the oxirane, thiirane or episulphoxide rings and the electron-rich aromatic group of the chiral solvent, which also may play an important role in the conformations of the 1:1 solvated species. The analysis of the relative importance, for the systems in question, of these and other secondary interactions between the solutes and the solvent necessarily need more systematic and specific studies.

EXPERIMENTAL

M.ps of the episulphoxides were determined with a Perkin-Elmer differential Scanning Calorimeter DSC-1B. Optical rotations of the optically active compounds were measured at the sodium D line on a Perkin-Elmer Polarimeter Mod. 141 in a 1 dm or 1 cm cell at 25 ± 1°. The ^{1}H NMR spectra were recorded in $CDCl_3$ solution on a JEOL JNM-C-60HL spectrometer in the internal lock mode with TMS as internal standard. For the ^{1}H NMR spectra in optically active solvent, a mixture of compounds **2** or **3**, (*R*)-(−) 2,2,2,-trifluoro-1-phenyl ethanol **1**, $[\alpha]_D^{25} - 39.1°$ (neat), lit.[15]. $[\alpha]_D^{25} - 41.18°$ (neat), and CCl_4 in 1:2:3 molar ratio were used. An iterative determination of the NMR best parameters was performed in every case by means of the LAOCN 3 program.[16]

Racemic episulphides (**2,a**)–(**2,e**) were obtained from the corresponding racemic oxiranes by reaction with potassium thiocyanate or with thiourea as described in the literature.[5]

Table 2. Physical and ^{1}H NMR data of optically active episulphoxides 3

Episulphoxides	Absolute Configuration	m.p. °C	$[\alpha]_D^{25}$	^{1}H NMR[a] δ				^{1}H NMR[a] J		
				H_k	R_1	R_2	R_3	J_{k2}	J_{k3}	J_{23}
(3,a)	(1S,2S)	oil	+95.3°[b]	2.97	1.21	2.00	2.71	9.54	9.99	-6.39
(3,b)	(1S,2S)	oil	+74.9 [c]	2.64	0.93	2.23	2.70	10.18	10.85	-6.44
(3,c)	(1S,2S)	72 [d]	+210.7 [e]	4.05	—	2.81	3.10	11.11	10.11	7.66
(3,d)	(2S,3S)	96 [f]	-317.0 [g]	4.21	—	3.94	—	11.25	-	—

[a] Solvent $CDCl_3$, internal standard TMS. [b] c = 0.771, cyclohexane. [c] c = 7.55, $CHCl_3$

[d] m.p. of the racemic episulphoxide : 67 °C. [e] c = 1.065, $CHCl_3$. [f] m.p. of the racemic episulphoxide : 102 °C. [g] c = 0.524, Ethanol.

Optically active episulphides (2,a)–(2,d) were synthesised starting from the corresponding optically active epoxides of known absolute configuration and optical purity, as described elsewhere.[17]

(S,S)-(−) trans-*Dimethyl episulphide* (2,e) of very low optical purity (about 2%) was supplied by Dr. N. Spassky. To obtain a sample of higher optical activity we used the reaction described in the literature for the *meso* isomer.[6] A soln of 0.13 moles of ethyl carbonate and 0.10 moles of (*R, R*)-(−) 2,3-butandiol, $[\alpha]_{546}^{20} - 14$ in which 0.15 g of Na metal had been dissolved, was heated under reflux for 5 hr, after which the EtOH was removed by slow distillation. The subsequent fractional distillation at low pressure of the soln gave a highly pure product (>99%, g.c. analysis) in 83% yield, b.p. 66–67° (0.6 mm), n_D^{20} 1.4192, $\alpha_D^{25} + 35.7°$ (neat, dm), which was immediately treated with potassium thiocyanate at 200–210°, to furnish the (*S, S*)-(−) *trans*-2,3 dimethyl episulphide in 63% yield; b.p. 54–55° (180 mm), $[\alpha]_D^{25} - 96.73°$ (neat), n_D^{20} 1.4648, NMR (CCl_4): δ 2.52 (H, m), 1.47 (Me, m); lit.:[18] $[\alpha]_D^{25} - 129.0°$ (neat), n_D^{25} 1.4587, d_4^{25} 0.8863.

Racemic and optically active episulphoxides 3 were obtained by oxidation of the corresponding racemic and optically active episulphides 2 with peroxybenzoic acid at −30°C in CH_2Cl_2 soln following the procedure of Kondo and Negishi.[7]

(1S, 2S) *Propylene episulphoxide* (3, a) was obtained as an oil from (*S*) propylene episulphide having $[\alpha]_D^{25} - 44.3°$ (neat); lit.[19] $[\alpha]_D^{10} - 51.2°$ (neat). The crude product was purified by distillation under high vacuum ($10^{-3} - 10^{-4}$ mm) at room temp. The distillate was collected in a trap cooled by liquid N_2.

(1S, 2S) *t-Butyl episulphoxide* (3, b) was obtained by oxidation of (*S*) t-butyl episulphide having $\alpha_D^{25} - 38.5°$ (neat, dm); lit.[20] $\alpha_D^{25} - 39°$ (neat, dm). The crude product was a viscous oil at room temp and was purified by fractional crystallisation at −60° from pentane solution.

(1S, 2S) *Styrene episulphoxide* (3, c) was obtained from the (S) styrene episulphide having $[\alpha]_D^{25} + 29.4$ ($c = 2.03$, cyclohexane); lit.[21] $[\alpha]_D^{25} - 15.7$ (heptane), 35.8% optical purity. By crystallisation of the crude product from ether-petroleum ether we obtained only an unstable and impure product, as clearly revealed by the TLC on silica, ether-petroleum ether as eluants (90:10). Pure optically active or racemic styrene episulphoxide was obtained as an insoluble part from the crude product of the reaction after washing several times with cold ether.

(2S, 3S) trans-*Stilbene episulphoxide* (3, d) was obtained from (*S, S*) *trans*-stilbene episulphide with $[\alpha]_D^{25} - 309.4°$.[17] It was purified by crystallisation of the crude product of the reaction from hexane-$CHCl_3$ (60:40).

All the elemental analyses of the optically active and racemic episulphoxides were in very good agreement with the expected values.

The physical properties and ^{1}H NMR data of the racemic and optically active episulphoxides 3 are reported in table 2.

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