Analysis of the Absolute Configuration of Chiral [^{16}O,^{17}O,^{18}O]Sulphate Monoesters by Fourier Transform Infrared Spectroscopy

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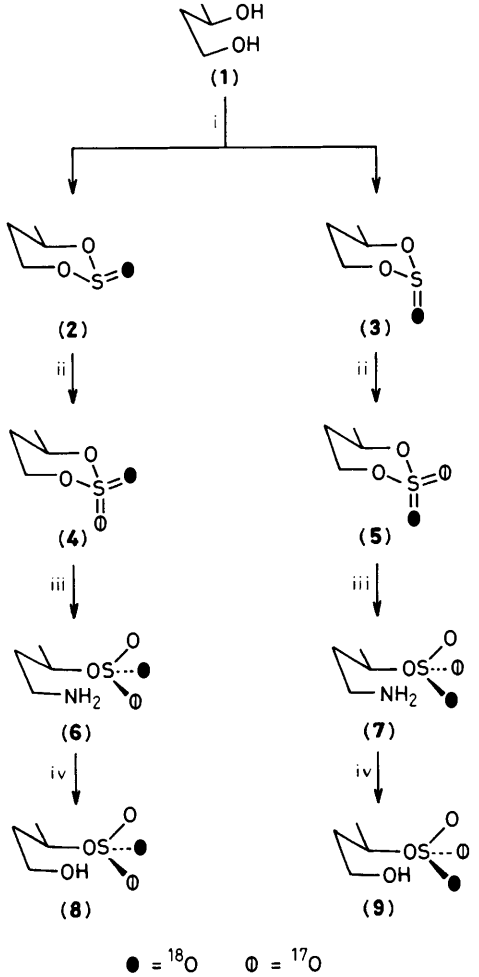
The symmetric and antisymmetric $>SO_2$ stretching region of the i.r. spectrum provides a means of distinguishing between (1*R*)-3-hydroxy-1-methylpropyl [(*S*)-^{16}O,^{17}O,^{18}O]sulphate and [(*R*)-^{16}O,^{17}O,^{18}O]sulphate after cyclisation to an isotopomeric mixture of (4*R*)-4-methyl-2,2-dioxo-1,3,2-dioxathianes.

A general approach for the synthesis of chiral [^{16}O,^{17}O,^{18}O]-sulphate monoester has been developed,[1] but in order to determine the stereochemical course of chemical and enzyme catalysed sulphuryl transfer reactions a method for their stereochemical analysis is also required. We now report a method of analysis using Fourier transform (F.t.) i.r. spectroscopy which depends on the crucial observation that heavy oxygen isotopes (^{17}O and ^{18}O) cause markedly different frequency shifts of the symmetric and antisymmetric $>SO_2$ stretching modes of 2,2-dioxo-1,3,2-dioxathianes when located in the axial and equatorial sites.[2]

(S_s)- and (R_s)-(1*R*)-3-Hydroxy-1-methylpropyl [^{16}O,-^{17}O,^{18}O]sulphates (**8**) and (**9**) were prepared as outlined in Scheme 1. [^{18}O]Thionyl chloride, prepared from sulphur [$^{18}O_2$]dioxide (99 atom% ^{18}O) and phosphorus pentachloride, was used to prepare the *cis*- and *trans*-(4*R*)-4-methyl-2-[^{18}O]oxo-1,3,2-dioxathianes (**2**) and (**3**) from (3*R*)-butane-1,3-diol (**1**).† The separated diastereoisomers were oxidised with ruthenium [^{17}O]tetraoxide (prepared *in situ* from ruthenium dioxide, sodium periodate, and [^{17}O]water). Since this oxidation is known to proceed with retention of configuration at sulphur,[3] the *cis*-[^{18}O]sulphite (**2**) gives the (2*S*)-compound (**4**) and the *trans*-[^{18}O]sulphite (**3**) gives the (2*R*)-compound (**5**).

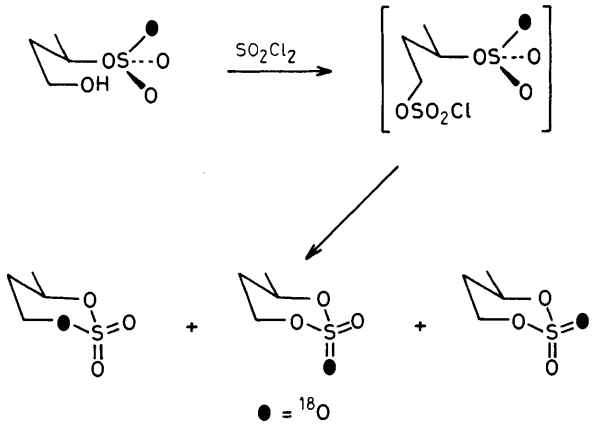


Scheme 1. The synthesis of the (S_s)- and (R_s)-sulphates (**8**) and (**9**). *Reagents:* i, $S^{18}OCl_2$, C_5H_5N; ii, $Ru^{17}O_4$ (from RuO_2, $NaIO_4$, and $H_2{}^{17}O$; iii, NH_3, MeOH; iv, $NaNO_2$, aq. AcOH.

The hydrolytic cleavage of 4-methyl-2,2-dioxo-1,3,2-dioxathiane has been extensively studied, but no conditions were found which gave exclusive cleavage of the primary C–O bond.[4] Ammonia in methanol, however, gave the desired mode of ring cleavage, the primary amines (**6**) and (**7**) being isolated virtually quantitatively. The corresponding primary alcohols (**8**) and (**9**) were obtained by treatment with nitrous acid in 83% yield.

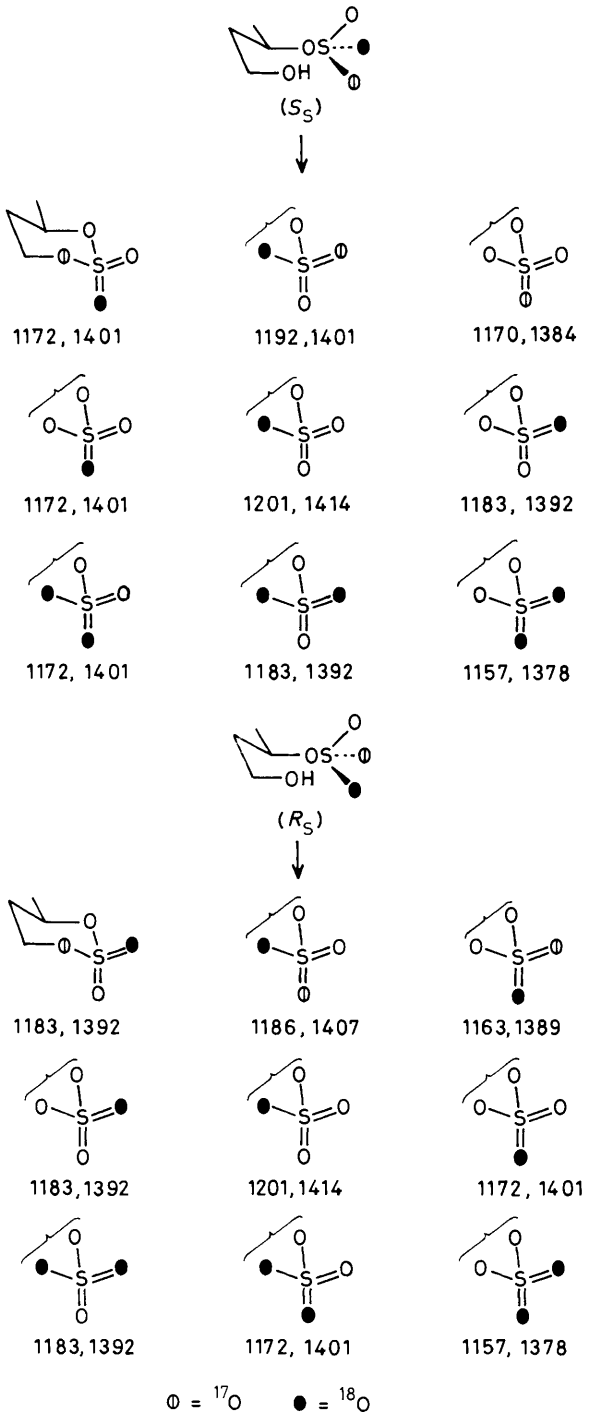
It was now necessary to develop a stereospecific method for the cyclisation of the enantiomeric [^{16}O,^{17}O,^{18}O]sulphate monoesters (**8**) and (**9**). Lack of precedent for the formation of cyclic sulphate esters from acyclic sulphate monoesters led to the exploration of several possible reagents. Only two were found, namely trifluoromethanesulphonic anhydride and sulphuryl chloride, the latter giving slightly better yields (*ca.* 40%).

In order to investigate whether there was any isotope exchange during cyclisation, (1*R*)-3-hydroxy-1-methylpropyl [^{18}O]sulphate was prepared (by the route outlined in Scheme 1



Scheme 2. The mechanism of cyclisation of (1*R*)-3-hydroxy-1-methylpropyl sulphate.

† (3*R*)-Butane-1,3-diol from Aldrich, $[\alpha]_D^{20}$ −22.05° (*c* 1, EtOH) contains 15% of the (3*S*)-enantiomer as determined by the method of R. C. Anderson and M. J. Shapiro, *J. Org. Chem.*, 1984, **49**, 1304. The highest recorded optical rotation for (3*R*)-butane-1,3-diol is $[\alpha]_D^{20}$ −31.6° (*c* 1, EtOH) by S. Murakami, T. Harada, and A. Tai, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1356.



Scheme 3. The cyclisation of the (S_S)- and (R_S)-sulphates (**8**) and (**9**) with retention of configuration at sulphur. If the three isotopes were fully enriched only the first three isotopomers of each set would be formed, but in practice the '^{17}O site' contains substantial amounts of ^{16}O and ^{18}O and consequently nine isotopomers should be formed for each chiral [^{16}O,^{17}O,^{18}O]sulphate. The frequency (cm^{-1}) of the symmetric and antisymmetric $>SO_2$ stretching bands for each isotopomer are shown below each formula.

except that in steps i and ii, $SOCl_2$ and $Ru^{18}O_4$ respectively were used) and cyclised with sulphuryl chloride. The chemical ionisation mass spectrum (NH_3) of the cyclic sulphate obtained revealed a molecular ion at *m/z* 172 only (M_r for $C_4H_8SO_4{\cdot}NH_4^+$ is 170 and $C_4H_8SO_3{}^{18}O{\cdot}NH_4^+$ is 172),

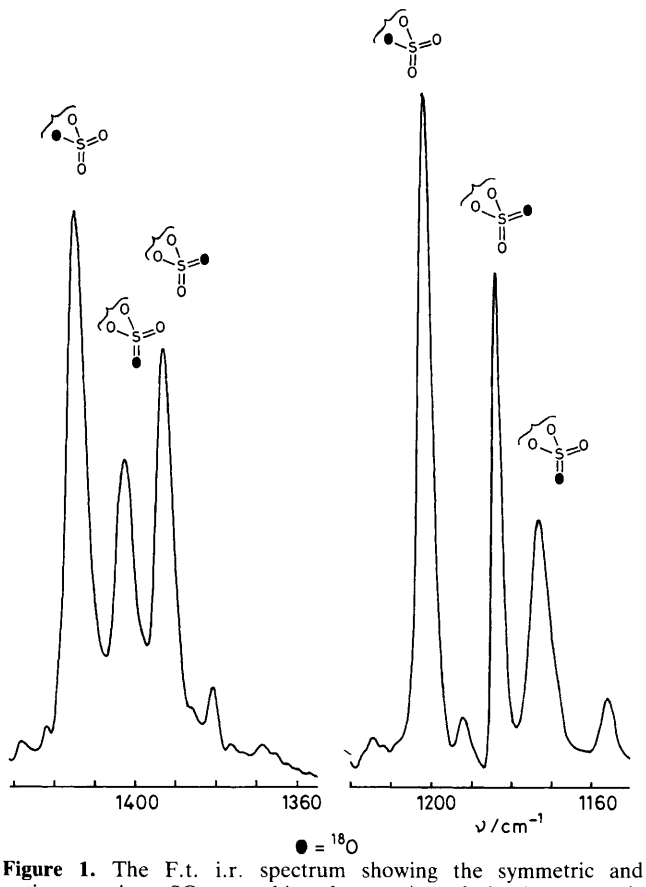


Figure 1. The F.t. i.r. spectrum showing the symmetric and antisymmetric $>SO_2$ stretching frequencies of the isotopomeric mixture obtained by cyclising (1*R*)-3-hydroxy-1-methylpropyl [^{18}O]sulphate with sulphuryl chloride. The spectrum was determined with a Perkin-Elmer 1750 F.t. i.r. spectrometer and a Perkin-Elmer 7300 Professional computer. The spectral resolution was enhanced by Fourier deconvolution: for the symmetric stretching region a line-width of 12 cm^{-1} and an enhancement factor of 1.5 were used whereas for the antisymmetric stretching region a line width of 20 cm^{-1} and an enhancement factor of 2.0 were used. The symmetric and antisymmetric $>SO_2$ stretching frequencies at 1201 and 1414 cm^{-1} respectively coincide with those for unlabelled (4*R*)-4-methyl-2,2-dioxo-1,3,2-dioxathiane. Only partial structures, showing the isotopic arrangement around sulphur, are illustrated.

suggesting that cyclisation had occurred by activating the primary alcohol followed by intramolecular displacement by the sulphate monoester (Scheme 2). This mode of cyclisation was confirmed by the natural abundance ^{13}C n.m.r. spectrum of the cyclic sulphate which showed C-1 to be split into two resonances at δ 71.784 and 71.749, the endocyclic ^{18}O causing an upfield shift of 0.035 p.p.m. as expected,[5] and in a 2 : 1 ratio of intensity after correcting for the ^{18}O enrichment of the sulphate monoester; thus no loss of isotope had occurred. It was now of interest to investigate the F.t. i.r. spectrum of the mixture of isotopomeric cyclic sulphate esters. As expected three absorption bands were observed in both the symmetric and antisymmetric $>SO_2$ stretching regions[2] (Figure 1). For the isotopomer containing ^{18}O in the C–O–S bridge the symmetric and antisymmetric $>SO_2$ absorption bands were at 1201 and 1414 cm^{-1} respectively, *i.e.* identical (at 1 cm^{-1} resolution) with those for (4*R*)-4-methyl-2,2-dioxo-1,3,2-dioxathiane (and consequently not resolved from a small amount of unlabelled material).[2] Thus a heavy oxygen isotope in the C–O–S bridge of the cyclic sulphate ester leaves both the symmetric and antisymmetric $>SO_2$ stretching frequencies unperturbed.

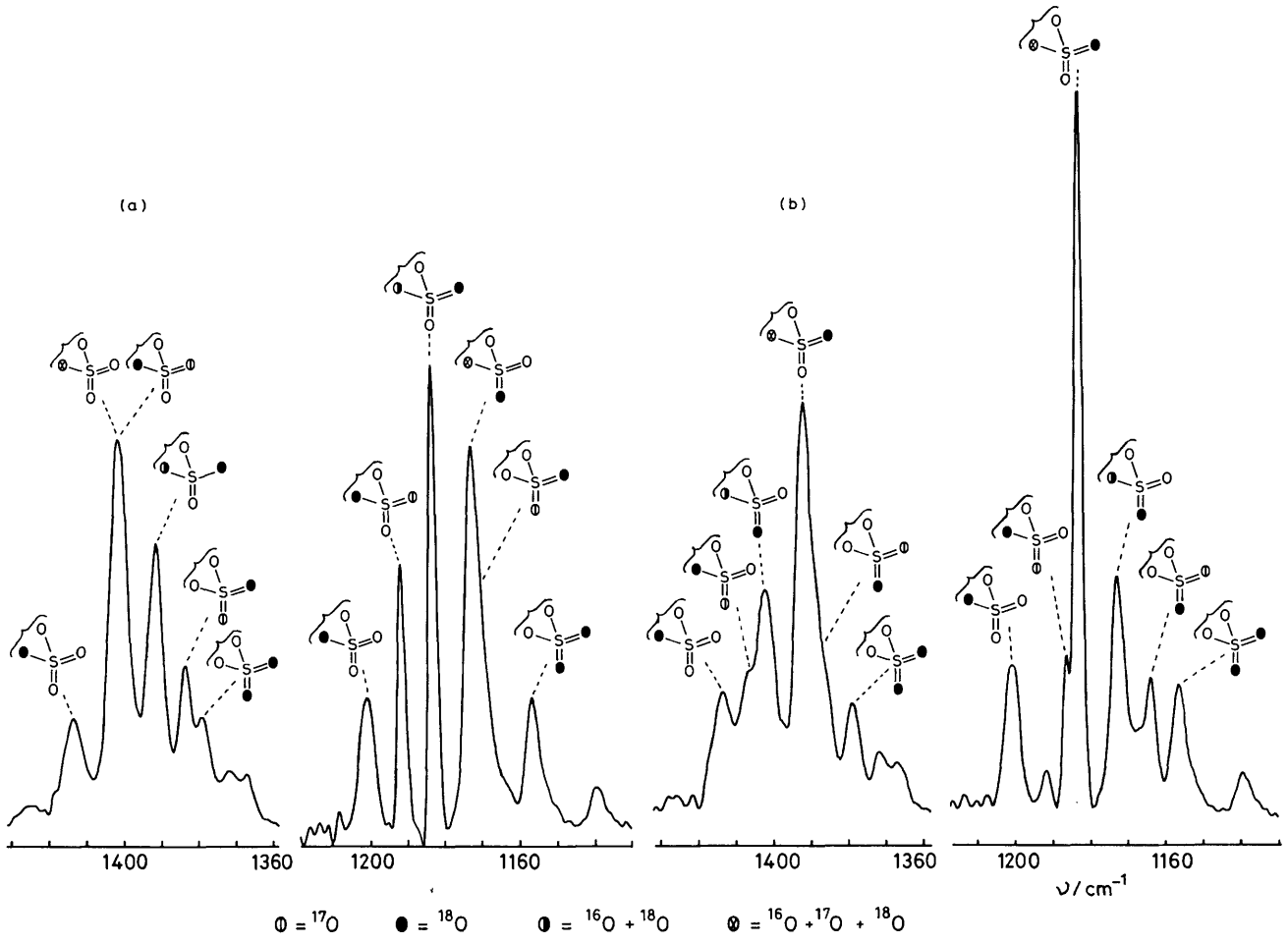


Figure 2. The F.t. i.r. spectra showing the symmetric and antisymmetric $>SO_2$ stretching frequencies of the isotopomeric mixture of 4-methyl-2,2-dioxo-1,3,2-dioxathianes obtained by cyclising with sulphuryl chloride: (a) the [(*S*)-^{16}O,^{17}O,^{18}O]sulphate (**8**) in which the '^{17}O-site' consists of 37.4 atom % ^{16}O, 36.4 atom % ^{17}O, and 26.2 atom % ^{18}O; (b) the [(*R*)-^{16}O,^{17}O,^{18}O]sulphate (**9**) in which the '^{17}O-site' consists of 36.0 atom % ^{16}O, 37.1 atom % ^{17}O, and 26.9 atom % ^{18}O. The spectra were determined as described in the legend to Figure 1. Only partial structures, showing the isotopic arrangement around sulphur, are illustrated.

Since none of the S–O bonds is broken in the cyclisation of (1*R*)-3-hydroxy-1-methylpropyl sulphate with sulphuryl chloride the cyclisation should proceed stereospecifically for a chiral [^{16}O,^{17}O,^{18}O]sulphate with retention of configuration. In order to confirm this prediction the [(*S*)-^{16}O,^{17}O,^{18}O]-sulphate ester (**8**) and the [(*R*)-^{16}O,^{17}O,^{18}O]sulphate ester (**9**) were cyclised with sulphuryl chloride and the F.t. i.r. spectra of the isotopomeric mixture of cyclic sulphate esters measured. The spectra of the symmetric and antisymmetric $>SO_2$ stretching frequencies are shown in Figure 2.

Scheme 3 shows the mixture of isotopomeric (4*R*)-4-methyl-2,2-dioxo-1,3,2-dioxathianes that should be formed by cyclising the (S_s)- and (R_s)-chiral [^{16}O,^{17}O,^{18}O]sulphate esters (**8**) and (**9**) with retention of configuration at sulphur by the mechanism outlined in Scheme 2. If all three isotopes were fully enriched only the three isotopomers shown on the top row of each set would be obtained, but in practice the '^{17}O-site' consists of a substantial amount of ^{16}O and ^{18}O, and therefore nine isotopomeric species should be formed; the ^{18}O site is 99 atom % ^{18}O. The symmetric and antisymmetric $>SO_2$ stretching frequencies are shown for each isotopomer.[2]

The spectra shown in Figures 2(a) and 2(b) are easily distinguishable, and therefore provide a method for the stereochemical analysis of chiral [^{16}O,^{17}O,^{18}O]sulphate esters.

It should be noted, however, that the line-width and extinction coefficient for different isotopomers are significantly different. This is well illustrated in Figure 1 where the [$^{18}O_{ax}$, $^{16}O_{eq}$]- and [$^{16}O_{ax}$,$^{18}O_{eq}$]-isotopomers must be present in equimolar amounts. If peak intensities were to be used to quantify the stereochemical analysis this fact must be taken into account. It is much simpler and more accurate to look for the presence and absence of the isotopomers containing ^{17}O in the symmetric $>SO_2$ stretching frequency region of the spectrum. In the set of isotopomers derived from the chiral [(*S*)-^{16}O,^{17}O,^{18}O]sulphate ester (**8**) the [$^{16}O_{ax}$,$^{17}O_{eq}$]-isotopomer (1192 cm^{-1}) should be well resolved whereas the [$^{17}O_{ax}$,$^{18}O_{eq}$] will not. In the set of isotopomers derived from the chiral [(*R*)-^{16}O,^{17}O,^{18}O]sulphate ester (**9**), the [$^{18}O_{ax}$,$^{17}O_{eq}$]-isotopomer (1163 cm^{-1}) should be well resolved whereas the [$^{17}O_{ax}$,$^{16}O_{eq}$]-isotopomer (1186 cm^{-1}) should be only partially resolved. Thus the enantiomeric excess can be calculated from the absorbance at 1192 and 1163 cm^{-1} after taking into account their relative extinction coefficients. In practice the analysis becomes more accurate by subtracting out the spectra of other isotopomers that contain weak bands

at these frequencies. The shoulder at 1163 cm^{-1} in Figure 2(a) and the small peak at 1192 cm^{-1} in Figure 2(b) arise because the (3*R*)-butane-1,3-diol used for the synthesis of the chiral [^{16}O,^{17}O,^{18}O]sulphate esters (**8**) and (**9**) contains 15% of the (3*S*)-enantiomer.† When this is taken into consideration, the cyclisation is seen to occur stereospecifically (within experimental error).

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