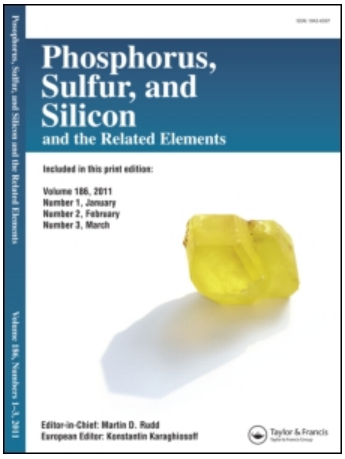

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THE STEREOCHEMICAL COURSE OF SULPHURYL TRANSFER REACTIONS

Gordon Lowe[a]
[a] Dyson Perrins Laboratory, Oxford University, Oxford, England

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THE STEREOCHEMICAL COURSE OF SULPHURYL TRANSFER REACTIONS

GORDON LOWE

Dyson Perrins Laboratory, Oxford University,
South Parks Road, Oxford OX1 3QY, England

Abstract A general strategy has been developed for the synthesis of chiral [^{16}O,^{17}O,^{18}O] sulphate monoesters of known absolute configuration and a method for determining the absolute configuration of chiral [^{16}O,^{17}O,^{18}O] sulphate monoesters by FT infrared spectroscopy has been established. Phenyl [^{16}O,^{17}O,^{18}O]sulphate has been synthesised and is being used to investigate the stereochemical course of chemical and enzyme-catalysed sulphuryl transfer reactions.

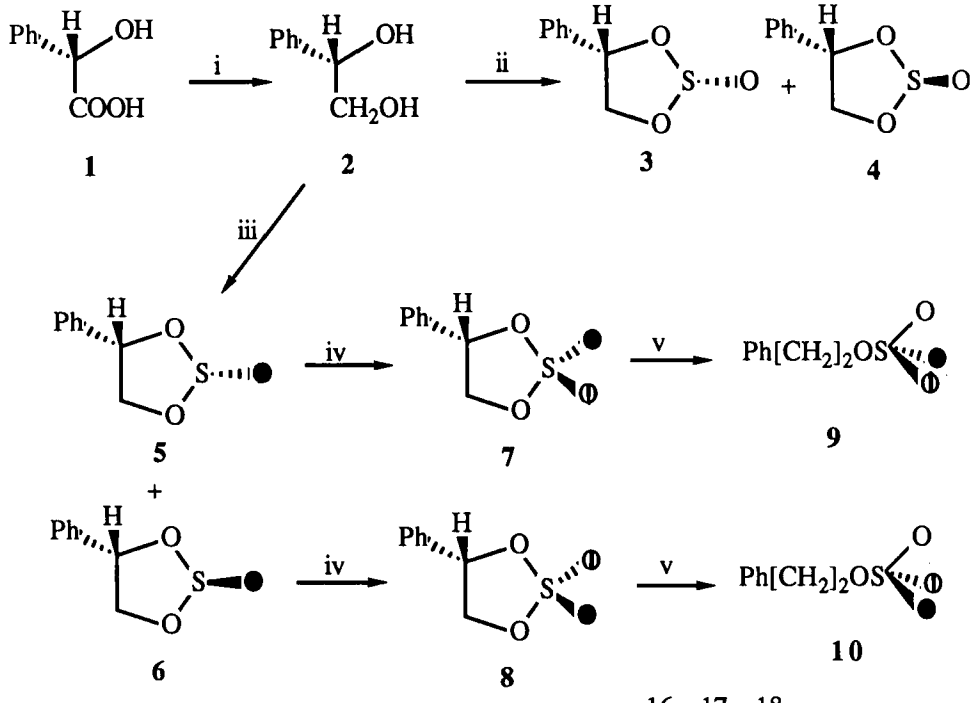
INTRODUCTION

Stereochemical analysis has long been recognised as a powerful mechanistic probe for both chemical and enzyme-catalysed reactions. However, when the reaction of interest occurs at a *pro-* or *pro-pro*-chiral centre, that centre must be made chiral, ideally by isotopic substitution. Prior to our studies on sulphate monoesters only two *pro-pro*-chiral centres had been made chiral by isotopic substitution, namely, methyl groups using ^{1}H, ^{2}H and ^{3}H,[1] and phosphate esters and anhydrides using ^{16}O,^{17}O and ^{18}O.[2] With a view to investigating the mechanism of chemical and enzyme-catalysed sulphuryl transfer reaction by stereochemical methods we have developed a general strategy for the synthesis of chiral [^{16}O,^{17}O,^{18}O] sulphate monoesters and a method for the determination of their absolute configuration.

SYNTHESIS AND STEREOCHEMICAL ANALYSIS OF CHIRAL [^{16}O,^{17}O,^{18}O] SULPHATE MONOESTERS.

In order to study the stereochemical course of sulphuryl transfer reactions we needed to develop a general strategy for the synthesis of chiral [^{16}O,^{17}O,^{18}O] sulphate monoesters of known absolute configuration and a method for their stereochemical analysis.

The general strategy for synthesis was to take a chiral 1,2- or 1,3-diol, convert it into the diastereoisomeric cyclic sulphites with [^{18}O]-thionyl chloride and then oxidise the sulphite esters to the cyclic sulphate esters with an [^{17}O]-labelled oxidant. Regioselective ring opening of the cyclic [^{17}O,^{18}O] sulphate diesters should give a chiral [^{16}O,^{17}O,^{18}O] sulphate monoesters of known absolute configuration. The first chiral [^{16}O,^{17}O,^{18}O] sulphate monoesters were prepared in this way as outline in Scheme 1.[3]



SCHEME 1. The synthesis of 2-phenylethyl (*S*)-[^{16}O,^{17}O,^{18}O]sulphate **9** and 2-phenylethyl (*R*)-[^{16}O,^{17}O,^{18}O]sulphate **10**. ⓪=^{17}O, ●=^{18}O; i, $LiAlH_4$; ii,$SOCl_2$; iii,$S^{18}OCl_2$; iv,RuO_2,$NaIO_4$,$H_2{}^{17}O$; v,$Bu^n{}_4N^+BH_4^-$

(*S*)-Mandelic acid **1** was reduced by lithium aluminium hydride to 2(*S*)-phenylethane-1,2-diol **2**, which on treatment with thionyl chloride gave the *cis*- and *trans*-2-oxo-4(*S*)-phenyl-1,3,2-dioxathiolanes **3** and **4**. Although their configurations could be assigned from spectroscopic evidence,[4] they were rigorously established by an X-ray crystallographic analysis of the *trans*-isomer.[5] [^{18}O]-Thionyl chloride was prepared from sulphur [$^{18}O_2$]-dioxide (99 atom % ^{18}O) and phosphorus pentachloride. Reaction of [^{18}O]-thionyl chloride with 2(*S*)-phenylethane-1,2-diol **2** gave *cis*-2-[^{18}O]oxo-4-(*S*)-phenyl-1,3,2-dioxathiolane **5** and *trans*-2-[^{18}O]oxo-4-(*S*)-phenyl-1,3,2-dioxathiolane **6** which were separated chromatographically. Their i.r. spectra had υ_{max} (CCl_4) (S=^{18}O) 1173 and 1177 cm^{-1} respectively whereas the unlabelled *cis* - and *trans* -diastereoisomers **3** and **4** had υ_{max} (CCl_4) (S=^{16}O) 1215 and 1222 cm^{-1} respectively. The oxidation of cyclic sulphites to sulphates with the incorporation of isotopic oxygen could not be accomplished by any literature procedure. We found, however, that ruthenium tetroxide was an effective oxidant and that if generated *in situ* from ruthenium dioxide by oxidation with sodium periodate, isotope could be incorporated from [^{17}O]- or [^{18}O]-water. The isotopically labelled water rapidly exchanges with periodate which is used to oxidise ruthenium dioxide to ruthenium tetroxide. Ruthenium tetroxide is soluble in chloroform so a two phase system can be used in which sodium periodate is dissolved in the isotopically labelled water and the sulphite to be oxidised in the chloroform. Since sodium periodate has a higher oxidation potential than ruthenium dioxide, only a catalytic amount of ruthenium dioxide is required. Oxidation of the separated diastereoisomers **5** and **6** with ruthenium [^{17}O]tetroxide generated *in situ* from ruthenium (IV) oxide, sodium periodate, and [^{17}O]-water (52.8 atom % ^{17}O, 9.4 atom % ^{16}O, 37. 8 atom % ^{18}O) in the presence of (ethanol free) chloroform, gave the diastereotopic 2(*R*)-[^{17}O,^{18}O]- and 2(*S*)[^{17}O,^{18}O]-dioxa-4(*S*)-phenyl-1,3,2-dioxathiolanes, **7** and **8** respectively; we have established that the oxidation with ruthenium tetroxide occurs with retention of configuration at sulphur.[6] Finally, reductive cleavage of the benzylic oxygen bond was achieved with tetrabutylammonium borohydride in dimethylformamide. Since this occurs without perturbing any of the sulphur to oxygen bonds the absolute configuration of the chiral [^{16}O,^{17}O,^{18}O]sulphate esters follows from the method of synthesis and the absolute configuration of (*S*)-mandelic

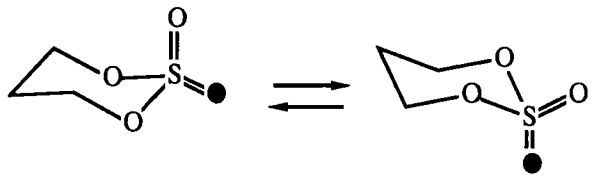
acid **1**. Thus, 2(*R*)-[^{17}O,^{18}O]dioxa-4(*S*)-phenyl-1,3,2-dioxathiolane **7** gives 2-phenylethyl (*S*)-[^{16}O,^{17}O,^{18}O]sulphate **9** and 2(*S*)-[^{17}O,^{18}O]dioxa-4-(*S*)-phenyl-1,3,2-dioxathiolan **8** gives 2-phenylethyl (*R*)-[^{16}O,^{17}O,^{18}O]sulphate **10** which were isolated as their crystalline tetrabutylammonium salts.

N.m.r. spectroscopy, which had been successfully used for the analysis of chiral [^{16}O,^{17}O,^{18}O]phosphate monoesters,[7] did not commend itself for the analysis of chiral [^{16}O,^{17}O,^{18}O]sulphate monoesters since none of the isotopes of sulphur possesses a nuclear spin quantum number of 1/2. Moreover the exocyclic oxygen atoms in a cyclic sulphate diester cannot be alkylated to render them chemically distinguishable as was possible with cyclic phosphate diesters. The analysis of chiral [^{16}O,^{17}O,^{18}O]sulphate monoesters presents, therefore, a new conceptual problem. We initially considered chiroptical methods, namely, vibrational circular dichroism and Raman optical activity and it was for this reason that we first made 2-phenylethyl (*S*)-[^{16}O,^{17}O,^{18}O]sulphate **9** and 2-phenylethyl (*R*)-[^{16}O,^{17}O,^{18}O]sulphate **10** as the chiral centre used to generate the chiral [^{16}O,^{17}O,^{18}O]sulphate monoesters was removed in the final stage of the synthesis leaving the [^{16}O,^{17}O,^{18}O]sulphate as the only chiral centre in these molecules. However, no chiroptical activity could be detected by either method in samples sent to several groups with expertise in these techniques.

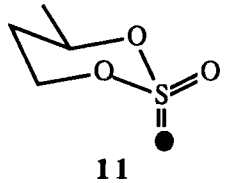
The frequency of an IR vibrational mode is markedly affected if isotopic substitution occurs in the functional group responsible. However, the magnitude of the isotope shift is difficult to predict except in the simplest of molecules, but the shift caused by replacing ^{16}O with ^{18}O in a functional group could theoretically be up to 40 cm^{-1}.[8] We expected that the generalised anomeric effect,[9] of the axial lone pairs of the ring oxygens on the axial exocyclic oxygen in 2,2-dioxo-1,3,2-dioxathianes, would ensure that the frequencies of the symmetric and antisymmetric >SO_2 vibrational modes were dependent on the location of the heavy oxygen isotope. If so, the isotope effect could form the basis of a method for the analysis of chiral [^{16}O,^{17}O,^{18}O]sulphate monoesters

In order to explore the influence of oxygen isotopic substitution at the axial and equatorial sites of six-membered cyclic sulphate esters, 2,2-[^{18}O]dioxo-1,3,2-dioxathiane was prepared from 2-oxo-1,3,2-dioxathiane by oxidation with ruthenium [^{18}O]tetroxide.[6] This should exist as an equimolar mixture of chair conformations (neglecting the equilibrium isotope effect) with ^{18}O in the axial and equatorial

sites,viz.



The FTIR spectrum is shown in Figure 1(a) (the ^{18}O site is only about 60% enriched). It is evident from this spectrum that the ^{18}O shift in both the symmetric and antisymmetric stretching modes of the $>SO_2$ group is conformationally dependent. It is also apparent that the isotope shift is greater and the intrinsic line-width smaller in the symmetric stretching mode; consequently this vibrational mode should be the most useful for analytical purposes. Separate deconvolution of these two spectral regions gave the resolution enhanced spectrum shown in Figure 1(b).
In order to assign the conformations responsible for the two symmetric and two antisymmetric $>S[^{16}O,^{18}O]$ absorption bands in 2,2-[^{18}O]dioxo-1,3,2-dioxathiane, and to confirm this observation, the *cis*- and *trans*-cyclic sulphite esters obtained by treating (3*R*)-butane-1,3-diol with thionyl chloride were oxidised with ruthenium [^{18}O]tetroxide to give the isotopomeric cyclic [^{18}O]sulphate esters. Since this oxidation is known to proceed with retention of configuration at sulphur,[6] the *cis*-sulphite must give the cyclic (R_S)-[^{18}O]sulphate **11** and the *trans*-sulphite must give the cyclic (S_S)-[^{18}O]sulphate **12**. As expected, the (R_S)-isotopomer **11** possesses only one symmetric (1172 cm^{-1}) and one antisymmetric (1401 cm^{-1}) $>S[^{16}O,^{18}O]$ stretching vibration and likewise the (S_S)-isotopomer **12** possesses only one symmetric (1183 cm^{-1}) and one antisymmetric (1392 cm^{-1}) $>S[^{16}O,^{18}O]$ stretching vibration, since the conformation with the methyl group equatorial should be preferred. Although these values differ slightly from those observed for 2,2-[^{18}O]dioxo-1,3,2-dioxathiane,the assignments shown in Figure 1 seem unambiguous.



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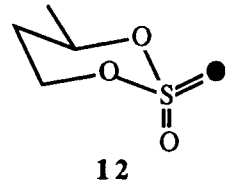

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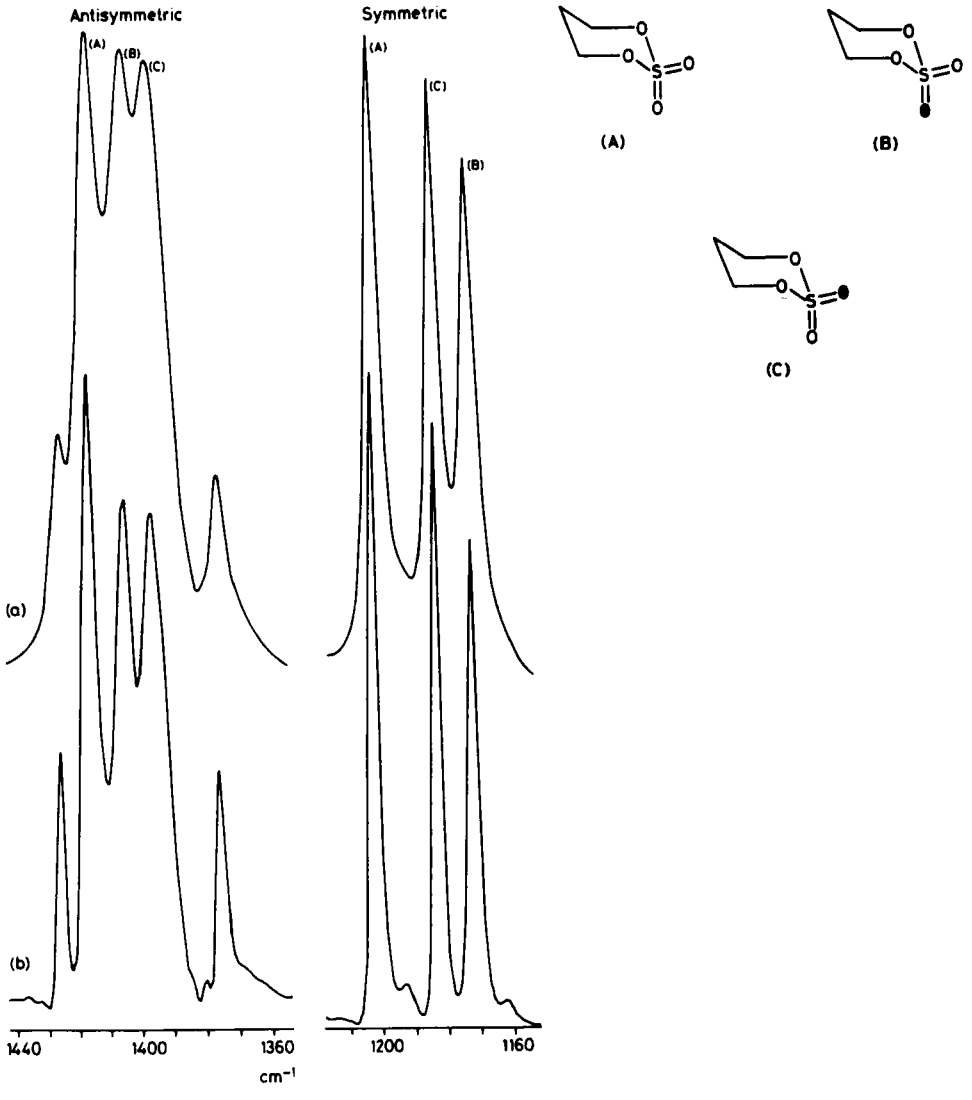


FIGURE 1. (a) The F.T.I.R. spectrum of the antisymmetric and symmetric >SO_2 stretching region of 2,2-[^{18}O]dioxo-1,3,2-dioxathiane and (b) the same spectrum after deconvolution with an enhancement factor of 1.68 and line-width at halfheight of 5 cm^{-1} for the antisymmetric >SO_2 stretching region and an enhancement factor of 1.50 and line-width at half height of 4 cm^{-1} for the symmetric >SO_2 stretching region.The spectra were measured on a Perkin-Elmer 1750 F.T.I.R. spectrometer at a resolution of 1 cm^{-1}.

The three stable oxygen isotopes, ^{16}O,^{17}O, and ^{18}O can be arranged to give nine exocyclic isotopomers of (4*R*)-4-methyl-2,2-dioxo-1,3,2-dioxathiane. Eight isotopomers have been prepared and their F.T.I.R. spectra determined and resolution-enhanced by deconvolution. The frequencies of the symmetric and antisymmetric stretching modes for each isotopomer are shown in Table 1.

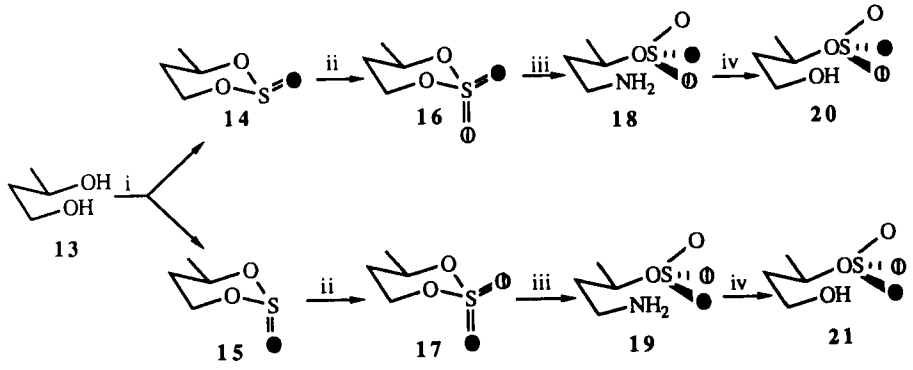
TABLE 1. The effect of oxygen isotopic substitution on the symmetric and antisymmetric $>SO_2$ stretching frequencies (cm^{-1}) of (4*R*)-4-methyl-2,2-dioxo- 1,3,2-dioxathianes. Δ is the isotope shift from the $>SO_2$ frequency.

Isotope		Symmetric stretching frequency	Δ for symmetric stretching mode	Antisymmetric stretching frequency	Δ for antisymmetric stretching mode
Axial	Equatorial				
^{16}O	^{16}O	1201	—	1414	—
^{16}O	^{17}O	1192	9	1401	13
^{17}O	^{16}O	1186	15	1407	7
^{16}O	^{18}O	1183	18	1392	22
^{18}O	^{16}O	1172	29	1401	13
^{17}O	^{18}O	1170	31	1384	30
^{18}O	^{17}O	1163	38	1389	25
^{18}O	^{18}O	1157	44	1378	36

There are a number of features about these data worthy of comment. First, the overall isotope shift is greater for the symmetric stretching mode (e.g. $>SO_2$ - $>S^{18}O_2$, 44 cm^{-1}) than for the antisymmetric stretching mode ($>SO_2$ - $>S^{18}O_2$, 36 cm^{-1}). Secondly, the shift caused by a heavy oxygen isotope in an axial position is greater than in an equatorial position for the symmetric stretching mode, but the reverse is observed in the antisymmetric stretching mode. Thirdly, the shift caused by ^{18}O is about double that caused by ^{17}O in the same site. Fourthly, the isotope shifts are approximately additive. Finally, since each of the diastereoisotopomeric pairs are distinguishable, especially in their symmetric stretching mode, I.R. spectroscopy should provide a means for analysing chiral

[^{16}O,^{17}O,^{18}O]sulphate monoesters after stereospecific cyclisation to a chirally substituted six-membered cyclic sulphate.

(S_S)- and (R_S)-(1*R*)-3-Hydroxy-1-methylpropyl [^{16}O,^{17}O,^{18}O]sulphates **20** and **21** were prepared as outlined in Scheme 2. [^{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 **14** and **15** from (3*R*)-butane-1,3-diol **13**.[10] The separated diastereoisomers were oxidised with ruthenium [^{17}O]tetroxide (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,[6] the *cis*-[^{18}O]sulphite **14** gives the (2*S*)-compound **16** and the *trans*-[^{18}O]sulphite **15** gives the (2*R*)-compound **17**.

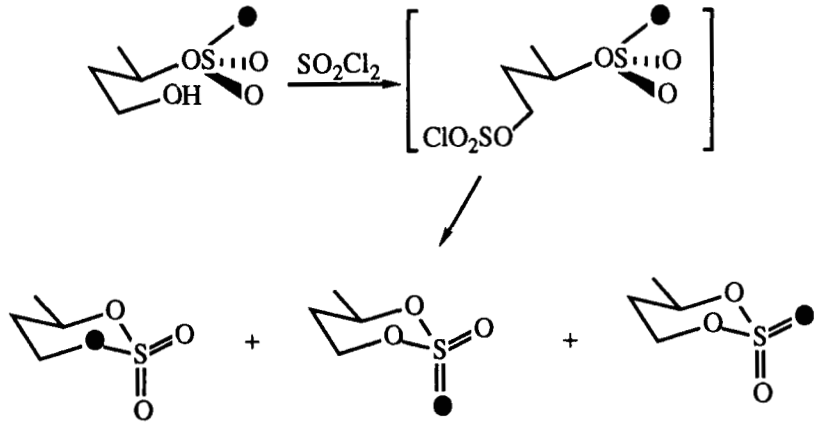


SCHEME 2. The synthesis of the (S_S)- and (R_S)-sulphates **20** and **21**. ⓪=^{17}O, ●=^{18}O; Reagents: i, $S^{18}OCl_2$,C_5H_5N; ii, $Ru^{17}O_4$ (from RuO_2, $NaIO_4$, and $H_2{}^{17}O$; iii, NH_3, MeOH; iv, $NaNO_2$, aq. AcOH.

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.[11] Ammonia in methanol, however, gave the desired mode of ring cleavage, the primary amines **18** and **19** being isolated virtually quantitatively. The corresponding primary alcohols **20** and **21** were obtained in 83% yield by treatment with nitrous acid.

It was now necessary to develop a stereospecific method for the cyclisation of the enantiomeric [^{16}O,^{17}O,^{18}O]sulphate monoester **20** and **21**. 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 a slightly better yield.

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 2, 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 $C_4H_8SO_4.NH_4^+$ is 170), suggesting that cyclisation had occurred by activating the primary alcohol followed by intramolecular displacement by the sulphate monoester (Scheme 3).



SCHEME 3. The mechanism of cyclisation of (1*R*)-3-hydroxy-methylpropyl sulphate. ●=^{18}O

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 O.O35 p.p.m. as expected,[12] 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 (Figure 2).

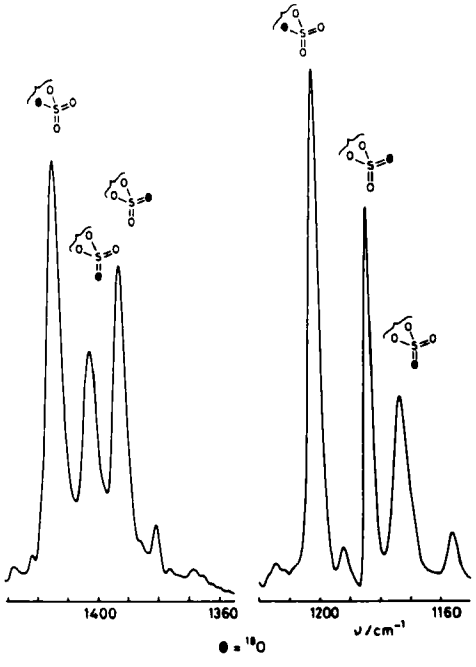


FIGURE 2. The F.T.I.R. spectrum showing the symmetric and antisymmetric >SO_2 stretching frequencies of the isotopomeric mixture obtained by cyclising (1*R*)-3-hydroxyl-1-methylpropyl [^{18}O]sulphate with sulphuryl chloride. The spectral resolution was enhanced by Fourier deconvolution: for the symmetric 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.

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). 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.

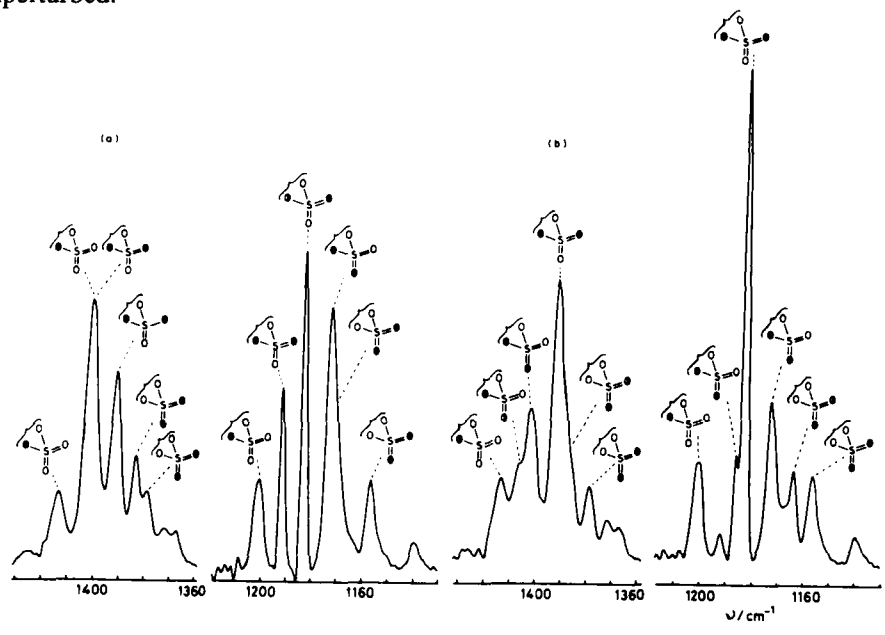
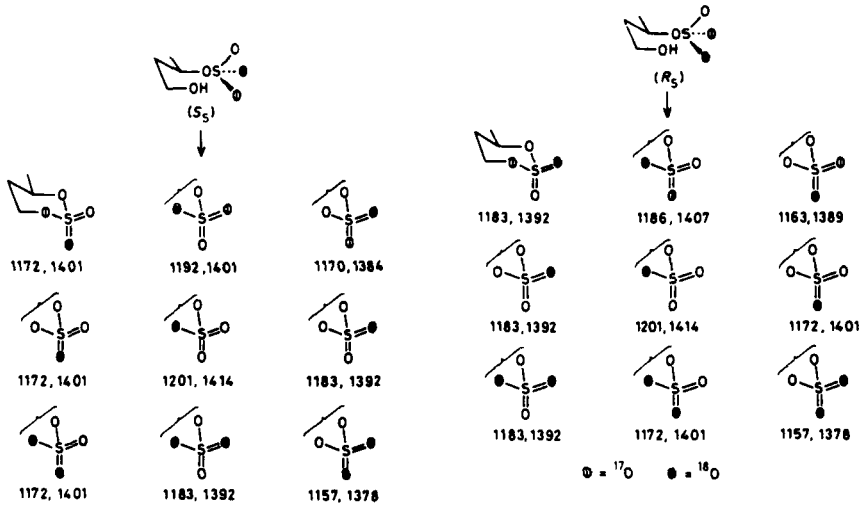


FIGURE 3. The F.T.I.R. spectra showing the symmetric and antisymmetric $>SO_2$ stretching frequencies of the isotopomeric mixture of 4-methyl-2,2-dioxo-1,3,2-dioxathianes obtained by cyclising with sulphuryl chloride: (a) the [(*S*)-^{16}O,^{17}O,^{18}O]sulphate **20** in which the '^{17}O-site' consists 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 **21** 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. ◐=^{17}O, ●=^{18}O, ◑=^{16}O+^{18}O, ⊗=^{16}O+^{17}O+^{18}O.

Since none of the S-O bonds are 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*)-^{15}O,^{17}O,^{18}O]-sulphate ester **20** and the [(*R*)-^{16}O,^{17}O,^{18}O]sulphate ester **21** 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 3.

Scheme 4 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 ester **20** and **21** with retention of configuration at sulphur by the mechanism outlined in Scheme 3.



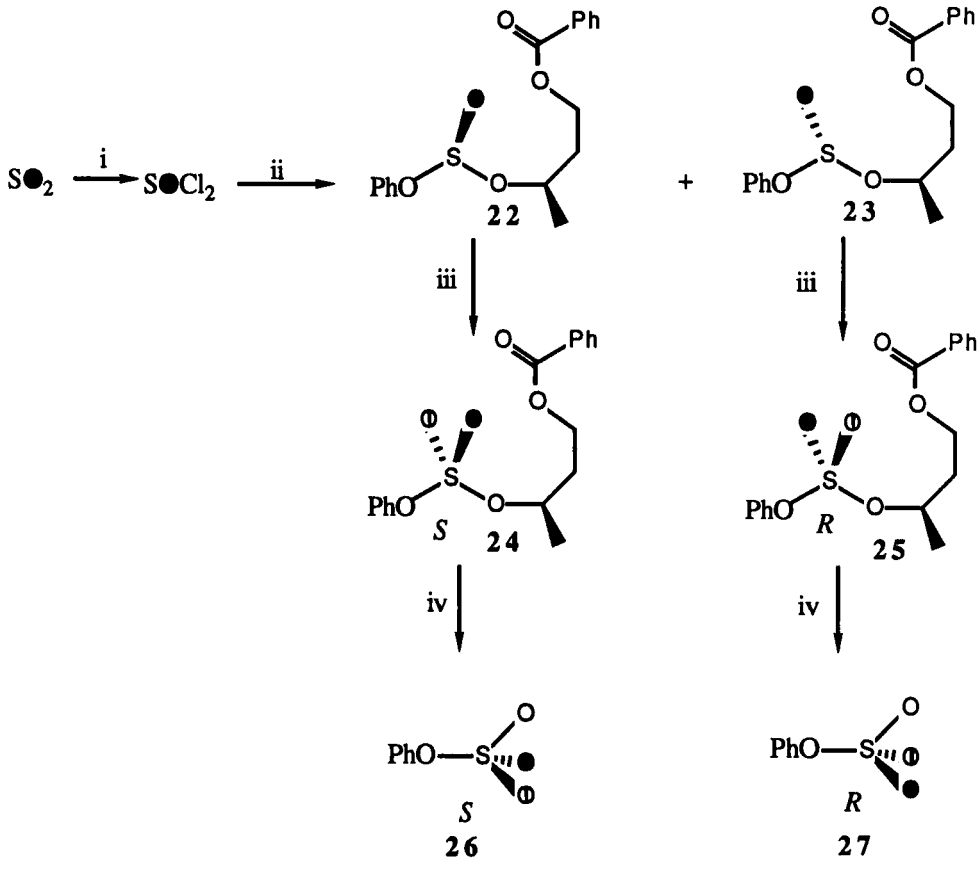
SCHEME 4. The cyclisation of the (S_S)- and (R_S)-sulphates **20** and **21** with retention of configuration at sulphur. If the three isotopes were fully enriched only the first three isotopomers of each set would be formed, but in practice the '^{17}O site' contains substantial amounts of ^{16}O and ^{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.

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.

The spectra shown in Figure 3(a) and 3(b) are easily distinguishable, and therefore provide a method for the stereochemical analysis of chiral [^{16}O,^{17}O,^{18}O]sulphate esters.[13] They also confirm that the cyclisation occurs stereospecifically (within experimental error) with retention of configuration at sulphur.

In order to study both chemical and enzyme catalysed sulphuryl transfer reactions phenyl [^{16}O,^{17}O,^{18}O]-sulphate of known absolute configuration was required. The route developed for the synthesis of enantiomeric phenyl [^{16}O,^{17}O,^{18}O]-sulphates and the method for their stereochemical analysis is outlined in Scheme 5. It was necessary for this synthesis that the [^{18}O]-thionyl chloride was pure and free of phosphorus oxychloride. An alternative method for the preparation of [^{18}O]-thionyl chloride was therefore developed involving the reaction of sulphur [$^{18}O_2$]-dioxide with 1,4-bis(trichloromethyl)benzene in the presence of a catalytic amount of ferric chloride.[14] After purification by distillation this was reacted first with phenol (one equivalent) and then with (3*R*)-butan-3-ol-1-benzoate (one equivalent) to give the diastereoisomeric [^{18}O]-sulphite esters **22** and **23.** Each diastereoisomeric ester was oxidised separately with ruthenium [^{17}O]-tetroxide. One of the [^{17}O,^{18}O]-sulphate diesters was then catalytically hydrogenolysed over Adam's catalyst to cleave the phenyl ester bond and then debenzoylated to give 3-hydroxy-1-methylpropyl [^{16}O,^{17}O,^{18}O]-sulphate, which was cyclized with sulphuryl chloride and analysed by FTIR. The FTIR spectrum, however, did not allow an unambiguous assignment of configuration at sulphur to be made, since it appears that some scrambling of label occurs during the hydrogenolysis, possibly by participation of the benzoyl ester to give an ion-pair intermediate which can return with positional isotope exchange.[15] This is being investigated further. Fortunately one of the sulphites forms low melting crystals and its structure will be examined by X-ray crystallography.

Alkyl oxygen fission of the [^{17}O,^{18}O]-sulphate diesters **24** and **25** to the enantiomeric phenyl [^{16}O,^{17}O,^{18}O]-sulphates **26** and **27** can be achieved by nucleophilic substitution with ammonia.The enantiomeric phenyl [^{16}O,^{17}O,^{18}O]-sulphates will be used to investigate the stereochemical course of both chemical and enzyme-catalysed sulphuryl transfer reeactions.



SCHEME 5 The synthesis of (R_S)- and (S_S) phenyl [^{16}O,^{17}O,^{18}O]sulphate **26** and **27**.
Reagents: i, 1,4-$C_6H_4(CCl_3)_2$, cat. $FeCl_3$; ii (a) PhOH, (b) (*R*)-$PhCOOCH_2CH_2CHMeOH$; iii, $Ru^{17}O_4$; iv, NH_3

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