Determination of the Chirality of Enantiomeric [^{16}O, ^{17}O, ^{18}O] Sulfate Esters by IR Spectroscopy: an *Ab Initio* Evaluation

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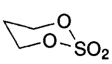
The calculated shifts accompanying oxygen isotopic substitution in the symmetric and antisymmetric $>SO_2$ stretching vibrational frequencies of 2,2-dioxo-1,3,2-dioxothianes confirm the experimental finding that these shifts can serve as a diagnostic tool for the determination of the absolute configuration at the sulfur centre of molecules containing chiral [^{16}O, ^{17}O, ^{18}O] sulfate groups.

Stereochemical studies are very useful in elucidating reaction mechanisms. When the reaction of interest takes place at a pro-prochiral centre, the chirality required to follow the reaction stereochemistry is preferably introduced by isotopic substitution.[1–3] This method is particularly attractive because the chirality of the stereochemical probe is achieved with minimal perturbation. However, the usual chiroptical methods of analysis are of no practical use in the determination of the chirality of such compounds and more sophisticated techniques have had to be devised.[1–3] To date, the isotopes of only two atoms have been used for the isotopic labelling of pro-prochiral centres: the isotopes of hydrogen (^{1}H, ^{2}H, ^{3}H)[1] and those of oxygen (^{16}O, ^{17}O, ^{18}O).[2–6]

In the case of isotopically labelled [^{16}O, ^{17}O, ^{18}O] sulfate groups, the problem of determining the chirality at the sulfur centre, of interest from the point of view of determining the stereochemical course of chemical- and enzyme-catalysed sulfuryl-transfer reactions, has been elegantly solved by Lowe and coworkers.[3–6] Lowe postulated[4] that, because of anomeric interactions in compounds like **1** and **2**, the isotopic shifts of the symmetric and antisymmetric SO_2 stretching frequencies would be dependent on the position (axial or equatorial) of the heavy oxygen isotopes. Consequently, if a chiral sulfate monoester were to be transformed to **2** *via* a series of reactions of known stereochemistry, then the absolute configuration of the former could, in principle, be deduced from an IR study of the resulting isotopomers of **2**. Indeed, Lowe developed such a route to cyclic sulfate esters.[7] In addition, he synthesized a series of isotopomers of **1** and **2** with known absolute configuration at the sulfur centres in order to obtain reference information on the isotopic shifts and to test his hypothesis.[5]

An alternative means of obtaining vibrational frequencies is through *ab initio* molecular orbital calculations.[8] The aim of the present study is to examine (*a*) whether an *ab initio* theoretical approach could have predicted beforehand if the method suggested by Lowe would be of practical value, and (*b*) whether theory could predict the isotopic shifts of the $>SO_2$ stretching frequencies to an accuracy sufficient to serve as a diagnostic fingerprint.

According to Lowe's hypothesis, the isotopomeric mixtures resulting from the cyclization of $\mathbf{3}_S$ and $\mathbf{3}_R$ (Scheme 1) can, in principle, be distinguished because they correspond to two different sets of isotopomers (**2a**, **2b**, **2c** for $\mathbf{3}_S$; **2a′**, **2b′**, **2c′** for $\mathbf{3}_R$)[5] where the components are present in equal proportions. In practice, the situation is complicated by the fact that the ^{17}O site is not 100% enriched but contains considerable amounts of ^{16}O and ^{18}O. This means that cyclization of **3** will result in the formation of nine isotopomers instead of three. However, as found experimentally[5] and also in agreement with our calculations, the frequencies of the $>SO_2$ stretches do not depend significantly on the oxygen isotopic substitution in the ring. This reduces the number of expected peaks in the IR spectrum of the isotopomeric mixture from nine to six. The overall result is that cyclization of $\mathbf{3}_S$ is expected to form the isotopomers with the exocyclic substitution patterns of **2a**, **2b**, **2c**, **2c′**, **2d** and **2e**, while $\mathbf{3}_R$ would produce **2a′**, **2b′**, **2c′**, **2c**, **2d** and **2e**.†



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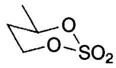

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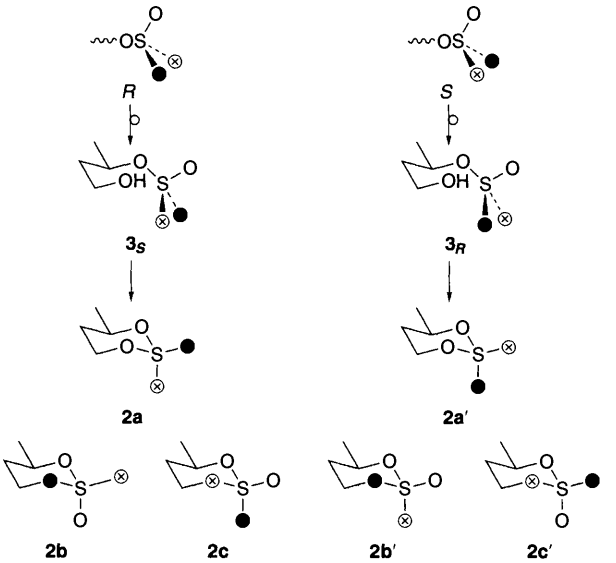
To establish an appropriate level of theory for the computational approach of the present study, we initially carried out *ab initio* molecular orbital calculations[8,9] on SO_2 and H_2SO_4. These showed[10] that an accurate description of geometries and vibrational frequencies requires high levels of theory and large basis sets. On the other hand, we found[10] that isotopic shifts can be reproduced at modest levels of theory. The results reported in this communication for isotopomers of **1**‡ correspond to calculations at the MP2 level of theory with the 6-31G* basis set.[8]

A technical problem arises in the case of calculations at low to medium levels of theory (*e.g.* HF/6-31G*, MP2/6-31G*) on H_2SO_4. The symmetric S=O stretch is (mis)calculated to lie quite close in frequency to the symmetric S–O–H bend.[10] For certain isotopomers, the two modes are sufficiently close so as to interact strongly.§ This artificial mixing alters the frequencies of both vibrational modes and also alters the related isotopic shifts, leading to misleading results. One solution to the problem is to use higher levels of theory, shifting the frequencies closer to their true values. Another is to ignore those off-diagonal elements of the force-constant matrix that give rise to the artificial coupling of different modes.¶ We have tried both approaches for H_2SO_4 and both are successful, giving essentially the same results.[10] In the case of **1**, where the problem of artificial mixing arises for both the symmetric and antisymmetric $>SO_2$ stretches, the use of significantly higher levels of



Scheme 1 Lowe's method[5] for determining the configuration of a chiral sulfur centre. The first step, which involves nucleophilic attack at sulfur by an alcohol, takes place with inversion of configuration, while the second step occurs with retention. The resulting isotopomers of **2** are classified according to their axial/equatorial oxygen isotopes as indicated also in Fig. 1 (O = ^{16}O; ⊗ = ^{17}O; ● = ^{18}O).

theory is not practical, and so only the second method has been applied.

Our calculated spectra (Fig. 1) have taken into account the incomplete isotopic enrichment in ^{17}O and have assumed a line width of 4 cm^{-1}. To facilitate comparison between theory and experiment, the peaks due to isotopomer **d** have been aligned in both spectra.† This was achieved by applying minor scaling corrections (0.993 for the symmetric stretch and 0.975 for the antisymmetric stretch) to all the calculated frequencies.

The similarity between the calculated and experimental IR spectra is very striking (Fig. 1), although the differing peak widths of the different isotopomers (not taken into account in the present theoretical treatment) affects the relative peak heights to some extent. Examination of Scheme 1 indicates that the isotopomeric mixture resulting from cyclization of $\mathbf{3}_S$ should give rise to peaks **a** and **b**, while peaks **a′** and **b′** should be absent, whereas the mixture resulting from cyclization of $\mathbf{3}_R$ should show the opposite picture. Focusing on these four peaks, we predict from our calculations that, in the region near the symmetric $>SO_2$ stretch, peaks **b** and **a′** should be well resolved and suitable for diagnostic use. Thus, the presence of peak **b** and the absence of peak **a′** in this part of the spectrum correlates with the *S* stereochemistry at the sulfur centre, whereas the reverse corresponds to the *R* configuration. In the region of the antisymmetric stretch, peak **a** is expected to be well resolved but **b′** less so, making interpretation of this region of the IR spectrum somewhat less definitive. The same conclusions were reached by Lowe and coworkers from their experimental study of the IR spectra of the stereospecifically synthesized reference compounds.[5]

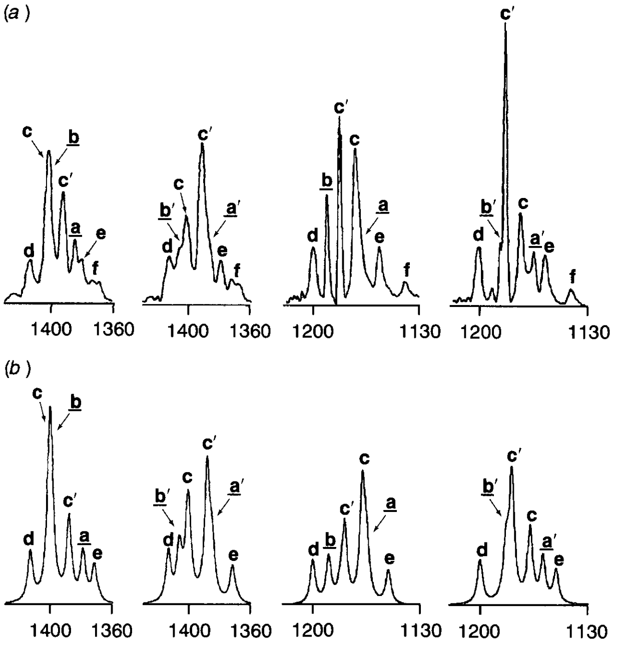


Fig. 1 (*a*) Portion of the experimental IR spectra showing the antisymmetric (*ca.* 1400 cm^{-1}) and symmetric (*ca.* 1200 cm^{-1}) $>SO_2$ stretches of the isotopomeric mixtures that result from cyclization of $\mathbf{3}_S$ (left) and $\mathbf{3}_R$ (right), as redrawn from ref. 5. (*b*) The corresponding calculated spectra for isotopomers of **1**. The curves were assumed to have a Lorentzian shape, with a line width of 4 cm^{-1}. Labels **a**–**e** indicate signals arising from different isotopomers, as drawn in Scheme 1, based on the oxygen isotopes at the axial and equatorial positions (O_{ax}/O_{eq}): **a**: $^{17}O/^{18}O$; **a′**: $^{18}O/^{17}O$; **b**: $^{16}O/^{17}O$; **b′**: $^{17}O/^{16}O$; **c**: $^{18}O/^{16}O$; **c′**: $^{16}O/^{18}O$; **d**: $^{16}O/^{16}O$; **e**: $^{18}O/^{18}O$. Peaks denoted by **f** were unassigned. The best diagnostic peaks are underlined.

We conclude that the computationally derived 'fingerprint' of Fig. 1 is in very good agreement with experiment. This implies that a computational approach could have demonstrated the feasibility of Lowe's hypothesis prior to carrying out relevant experiments. Furthermore, the correct absolute configuration at the sulfur centre of unknown systems could have been predicted from the relevant IR spectra with high confidence using the computational results, thus obviating the need for the stereospecific synthesis of appropriate reference molecules.

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Footnotes

† Isotopomers **d** and **e** have ^{16}O and ^{18}O, respectively, in both axial and equatorial positions.

‡ For simplicity, calculations were carried out for isotopomers of **1** rather than **2**. It has been found experimentally[5] that the isotopic shifts in the $>SO_2$ stretching frequencies of **1** and **2** agree to within 1–2 cm^{-1}.

§ The symmetric S–O–H bend is found experimentally to lie 100 cm^{-1} below the symmetric S=O stretch whereas at the MP2/6-31G* level of theory this difference is calculated to be only 28 cm^{-1}. Since the effect of oxygen isotopic substitution on the symmetric stretch can be up to approximately 40 cm^{-1}, it is clear that for certain isotopomers the two modes lie sufficiently close in energy so as to mix strongly.

¶ Neglecting the off-diagonal elements of the force constant matrix is found to have only a small effect (less than 1%) on the calculated $>SO_2$ stretching frequencies.

References

1 J. W. Cornforth, J. W. Redmond, H. Eggerer, W. Buckel and C. Gutschow, *Nature*, 1969, **221**, 1212; J. Lüthy, J. Rétey and D. Arigoni, *Nature*, 1969, **221**, 1213; H. G. Floss and M.-D. Tsai, *Adv. Enzymol. Relat. Areas Mol. Biol.*, 1979, **50**, 243.
2 J. R. Knowles, *Annu. Rev. Biochem.*, 1980, **49**, 877; G. Lowe, *Acc. Chem. Res.*, 1983, **16**, 244.
3 G. Lowe, *Phosphorus Sulfur Silicon Relat. Elem.*, 1991, **59**, 63.
4 G. Lowe and M. J. Parratt, *J. Chem. Soc., Chem. Commun.*, 1985, 1073.
5 G. Lowe and M. J. Parratt, *Bioorg. Chem.*, 1988, **16**, 283.
6 For applications of the method see: C. L. L. Chai, T. W. Hepburn and G. Lowe, *J. Chem. Soc., Chem. Commun.*, 1991, 1403; C. L. L. Chai, W. A. Loughlin and G. Lowe, *Biochem. J.*, 1992, **287**, 805; C. L. L. Chai and G. Lowe, *Bioorg. Chem.*, 1992, **20**, 181.
7 G. Lowe and S. J. Salamone, *J. Chem. Soc., Chem. Commun.*, 1984, 466.
8 W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986.
9 M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. DeFrees, J. Baker, J. J. P. Stewart and J. A. Pople, GAUSSIAN92, Gaussian Inc., Pittsburgh, PA, 1992.
10 A. Nicolaides and L. Radom, to be published.