local dipole–dipole interactions, and packing requirements.[48] The relevance of these results to complexes in solution is uncertain, but they at least demonstrate that orientations of the type suggested here are possible.

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(48) S. C. Wallwork and C. J. Timmons, Abstracts, 7th International Congress and Symposium of the International Union of Crystallography, Moscow, July, 1966, *Acta Cryst. Suppl.*, **21**, A133 (1969).

Nucleophilic Substitution at Tetracoordinate Hexavalent Sulfur. The Reaction of (−)-Menthyl Phenylmethanesulfonate with *p*-Tolylmagnesium Bromide[1]

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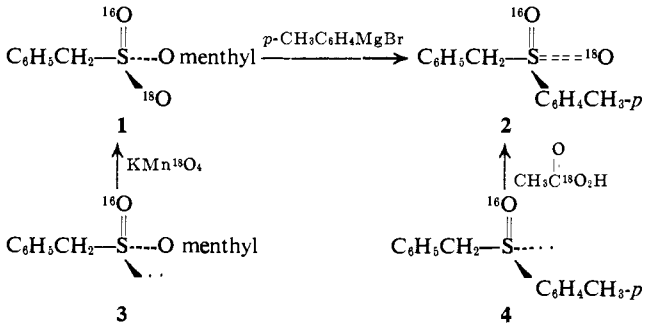
Abstract: Menthyl phenylmethanesulfinate of configuration *R* at sulfur was stereospecifically oxidized to menthyl phenylmethanesulfonate with 90.2% ^{18}O potassium permanganate. Treatment of this sulfonate ester with *p*-tolylmagnesium bromide gave (−)-benzyl *p*-tolylsulfone-^{16}O,^{18}O, presumably of configuration *S*. Since the levorotatory sulfone had been prepared by oxidation of (*R*)-benzyl *p*-tolylsulfoxide, the reaction of the sulfonate ester with the Grignard reagent proceeded with inversion of configuration at sulfur. This constitutes the first example in which the stereochemistry of nucleophilic substitution at tetracoordinate hexavalent sulfur has been established.

This article describes the stereochemistry of a nucleophilic substitution reaction of tetracoordinate hexavalent sulfur, *i.e.*, the reaction of a sulfonate ester with a Grignard reagent to form a sulfone (Scheme I, **1** → **2**). To the best of our knowledge, this is the first time that the stereochemistry of nucleophilic substitution at tetracoordinate hexavalent sulfur has been established.[3] The reaction sequence used in our study is shown in Scheme I.

Scheme I



Menthyl phenylmethanesulfinate (**3**) of configuration *R* at sulfur was oxidized to menthyl phenylmethanesulfonate (**1**) using potassium permanganate (90.2% ^{18}O) in acetone.[4] The resulting sulfonate ester was treated with *p*-tolylmagnesium bromide to give optically active benzyl *p*-tolylsulfone-^{16}O,^{18}O (**2**). In the pioneering paper demonstrating the use of ^{18}O in sulfur stereochemical studies, Stirling[5] oxidized (*R*)-benzyl *p*-tolylsulfoxide (**4**) to sulfone **2** utilizing ^{18}O-labeled peracetic acid. Both the sulfone obtained by us (**1** → **2**) and by Stirling (**4** → **2**) were levorotatory in chloroform and thus of the same configuration. If both oxidations **3** → **1** and **4** → **2** follow the same stereochemical path, then the reaction of the stereospecifically ^{18}O labeled sulfonate ester **1** with *p*-tolylmagnesium bromide to give sulfone **2** proceeds with *inversion of configuration at tetracoordinate hexavalent sulfur.*

There is evidence from similar systems that both potassium permanganate and peracids oxidize tricoordinate tetravalent sulfur to tetracoordinate hexavalent sulfur with the same stereochemistry (eq 1). In earlier work,[6] we oxidized (−)-S-methyl-S-*p*-tolyl-N-*p*-toluenesulfonylsulfilimine (**5**) to (−)-S-methyl-S-*p*-tolyl-N-*p*-toluenesulfonylsulfoximine (**6**) using potassium permanganate in pyridine. Subsequently, Rayner, von Schriltz, Day, and Cram[7] carried out the

(1) We acknowledge with gratitude support by the National Science Foundation (GP 8136 and GP 5283).

(2) This work is from the Ph.D. thesis of M. A. S., University of New Hampshire, 1968.

(3) Our assignment of the sulfur atom's covalency follows from consideration of compounds in which the ligands are monovalent fluorine or divalent oxygen atoms. The coordination number is the number of ligands. This system in which both the coordination number and covalency are designated avoids certain ambiguities in terminology; *e.g.*, the sulfur atoms in sulfones and sulfur tetrafluoride are both tetracoordinate but in the former the sulfur is hexavalent and in the latter, tetravalent.

(4) The configurations of **3** and **4** were established through the work of K. Mislow and coworkers. For a leading reference see M. Axelrod, P. Bickart, J. Jacobus, M. M. Green, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4835 (1968).

(5) C. J. M. Stirling, *J. Chem. Soc.*, 5741 (1963).

(6) M. A. Sabol, R. W. Davenport, and K. K. Andersen, *Tetrahedron Lett.*, 2159 (1968).

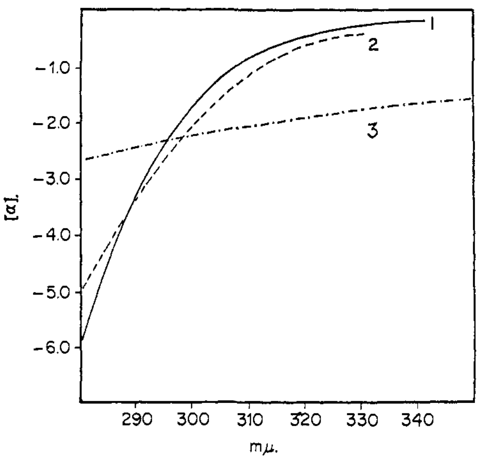
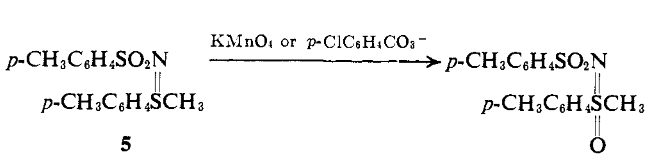


Figure 1. Optical rotatory dispersion curves for benzyl *p*-tolylsulfone (**2**) (curve 1), Stirling's benzyl *p*-tolylsulfone (curve 2), (−)-menthol and (−)-menthyl phenylmethanesulfonate (both curve 3) in chloroform. The curve for Stirling's sulfone has been increased by a factor of 4.0, the curve for (−)-menthol reduced by 10^{-2}, and the curve for the sulfonate ester reduced by 7.75×10^{-3}.



5 6 (1)

same reaction using *m*-chloroperbenzoate anion as the oxidant. Since both groups obtained (−)-**6** from (−)-**5**, both reagents oxidized the tricoordinate tetravalent sulfur in a stereochemically identical manner. If we make the reasonable assumption that such oxidations proceed with retention, then we can assign configurations to sulfonate ester **1** and sulfone **2**. Indeed, Stirling made this assumption and assigned the S configuration to sulfone **2**. Sulfonate ester **1** would have configuration S at sulfur.[8]

We should emphasize that the conclusion that reaction **1** → **2** proceeds with inversion is independent of the stereochemistry of the oxidations **3** → **1** or **4** → **2**. The only requirement is that they both have the same stereochemistry.

The reaction of sulfonate esters with Grignard reagents can lead to a variety of products depending on the nature of the ester and the Grignard. Typically, the Grignard substitutes at carbon and one gets alkylation (eq 2).[9] In order to get attack at sulfur, a system in which substitution at carbon or β elimination cannot readily occur must be chosen. Sulfonate ester **1**

$$RSO_2OR' + R''MgX \longrightarrow R'R'' + RSO_3MgX \qquad (2)$$

in which the CO bond is equatorial fulfills these requirements.

One could imagine that substitution at sulfur in the case of sulfonate ester **1** proceeded by sulfene formation (eq 3) with the Grignard acting as a base. Reaction of

$$C_6H_5CH_2SO_2OR \xrightarrow{p\text{-}CH_3C_6H_4MgBr} C_6H_5CH{=}SO_2 \qquad (3)$$
$$\mathbf{7}$$

7 with the Grignard would then lead to the sulfone **2**. Since **7** is isoelectronic with sulfur trioxide, it should be planar and the sulfone produced from it inactive. Since the sulfone which we isolated is levorotatory, this mechanism is ruled out.

The optical rotation of sulfone **2** is extremely small, so the question naturally arises whether the rotation which we observed is actually due to the sulfone or perhaps rather to some levorotatory impurity. The methods we used to ensure that sulfone **2** was free from optically active impurities are based on the procedures used by Stirling to purify the same sulfone. Suitable blank experiments conducted on unlabeled normal ^{16}O materials convinced us of the validity of these procedures.

Four possible contaminants were of principal concern. They are sulfonate ester **1**, menthol, sulfinate ester **3**, and sulfoxide **4**. The first two are levorotatory; the latter two are dextrorotatory. Sulfinate ester **3** would be present in the starting sulfonate ester **1** as a result of incomplete oxidation in step **3** → **1**. Some if not all of this unoxidized ester (**3**) would yield sulfoxide **4** when step **1** → **2** was carried out.

Sulfone **2** was isolated by column chromatography on silica gel with chloroform after which it was boiled several times with fresh portions of petroleum ether (bp 30–65°). Stirling showed that this procedure removed menthol as well as (−)-menthyl *p*-toluenesulfinate, his precursor for sulfoxide **4**, from sulfone **2**. When we synthesized isotopically normal sulfone **2** from *p*-tolylmagnesium bromide and isotopically normal sulfonate ester **1**, prepared from α-toluenesulfonyl chloride and menthol, and subjected this sulfone to the chromatography and petroleum ether extractions eventually used for purifying ^{18}O-labeled sulfone **2**, we found it to be optically inactive. This verifies Stirling's procedure for the removal of (−)-menthol and shows that any unreacted sulfonate ester **1** is removed as well. It is quite likely that traces of sulfinate ester **3** are also removed since Stirling showed that a structurally similar sulfinate ester, (−)-menthyl *p*-toluenesulfinate, was removed by this procedure.

At this point any contaminating sulfoxide **4** was reduced to optically inactive benzyl *p*-tolylsulfide by treatment with titanium(III) chloride. Then several extractions with petroleum ether were used to remove the sulfide.

After these purification steps, sulfone **2** gave a negative plain ORD curve which was not superimposable on the negative plain ORD curves of unlabeled sulfonate ester **1** or of (−)-menthol (Figure 1).

The mass spectrum of ^{18}O-labeled sulfone **2** gave a molecular ion peak at *m/e* 248 while the unlabeled sulfone gave a peak at *m/e* 246. From a consideration of peak heights, we conclude that our labeled sulfone is 83.5% isotopically pure.

Stirling reported that his ^{18}O-labeled sulfone was not less than 80% isotopically pure and had a rotation, $[\alpha]_D$, of $-0.16 \pm 0.05°$. The small amount of our ^{18}O-labeled sulfone precluded a measurement of its rotation at the sodium D line. Professor Stirling

(7) D. R. Rayner, D. M. von Schriltz, J. Day, and D. J. Cram, *J. Amer. Chem. Soc.*, **90**, 2721 (1968).

(8) By convention, in assigning a priority to the group around sulfur prior to application of the sequence rule, only octet structures are considered and the SO or SN double bonds in our stereochemical formulas are replaced by single bonds: R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem. Int. Ed. Engl.*, **5**, 385 (1966).

(9) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall Inc., Englewood Cliffs, N. J., 1954, pp 1278–1284.

kindly sent us his remaining sample of labeled sulfone. Unfortunately, the sample container broke during transit necessitating recovery of the sulfone by chloroform extraction followed by chromatographic purification on silica gel followed by several recrystallizations from absolute ethanol. The purified sulfone gave a negative plain curve from 350 to 280 mμ (Figure 1), and was 80% isotopically pure. This curve was similar in shape to that observed for our ^{18}O-sulfone, but only of one quarter the magnitude. At worst this could mean that both samples were contaminated to differing extents by some levorotatory impurity. On the other hand, Stirling's sulfone had been stored in a chloroform solution for many months before we measured its rotation. Perhaps it partially racemized in some as yet undetermined way. If our work and that of Stirling's has successfully removed interferring optically active impurities, then both sulfones must have the same configuration. This substantiates our conclusions concerning the stereochemical course of the substitution reaction 1 → 2.

Experimental Section

Optical rotations were measured on a Cary Model 60 recording spectropolarimeter. In general all rotations were measured in the region from 400 to 300 mμ as well as in the region from 500 to 600 mμ. Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6E mass spectrometer.

(−)-Menthyl Phenylmethanesulfonate. Phenylmethanesulfonyl chloride (25 g, 0.13 mol) and (−)-menthol (20 g, 0.13 mol) were dissolved in anhydrous ether and cooled in an ice–salt bath. Anhydrous pyridine (20 g, 0.25 mol, 21 ml) in anhydrous ether was added dropwise over a 4.5-hr period. After the white, crystalline pyridine hydrochloride was removed by filtration, the solvent was removed under reduced pressure. An oil remained which crystallized on standing. The product (26 g, 59%) was obtained as white crystals, mp 64–65.5° (lit.[10] mp 66–67°) from ether, $[\alpha]_D$ +55° (*c* 1.13, chloroform).

(−)-Menthyl phenylmethanesulfinate was prepared from (−)-menthol, phenylmethanesulfinyl chloride, and pyridine in ether and recrystallized from ethanol (65% yield), mp 72–75°, $[\alpha]_D$ +105° (*c* 2.0, chloroform) (lit.[4,11] mp 75.7–76.5°, $[\alpha]_D$ +105° in chloroform).

(−)-Menthyl Phenylmethanesulfonate from (−)-Menthyl Phenylmethanesulfinate. (−)-Menthyl phenylmethanesulfinate (0.934 g, 0.00316 mol) was dissolved in a minimum amount of acetone and added dropwise at room temperature to a solution of 0.500 g (0.00316 mol) of potassium permanganate in 40 ml of acetone. The mixture was stirred for 2 days, the reaction mixture was centrifuged, and the clear liquid decanted. The manganese dioxide was washed with acetone and centrifuged and all of the decanted liquids were combined. The solvent was removed under reduced pressure. The crystals that were obtained from the remaining yellow oil were dissolved in a minimum amount of chloroform and chromatographed on a column (32 × 3.0 cm) of silica gel (Fisher, Powder) using spectral grade chloroform as the eluent. The product (0.435 g, 45.5%) was collected as white crystals, mp 64–65.5° (lit.[10] mp 66–67°).

When the above procedure was carried out using exactly the same quantities but employing ^{18}O-labeled potassium permanganate (90.2 atom % ^{18}O obtained from Miles Laboratories, Elkhart, Ind.), a 44.5% yield of ^{18}O-labeled sulfonate ester was obtained, mp 64.5–66°.

Benzyl *p*-Tolylsulfone. A Grignard reagent prepared from *p*-bromotoluene (5.3 g, 0.031 mol) and dried magnesium turnings (0.75 g, 0.031 g-atom) in anhydrous ether (50 ml) was titrated with 1.00 *N sec*-butyl alcohol in xylene using 1,10-phenanthroline as an indicator. The solution was found to contain 0.00060 mol of Grignard reagent per milliliter.

The Grignard reagent (5.0 ml, 0.0031 mol) was added over a period of 10 min to a solution of (−)-menthyl phenylmethanesulfonate (0.96 g, 0.0031 mol) which had been heated to reflux. The addition was carried out under a slow stream of sulfuric acid–dried nitrogen. After stirring at reflux for 1.5 hr, the mixture was cooled to 0° and hydrolyzed with a saturated solution of ammonium chloride. The salts were removed by filtration and washed with ether. The combined ether layers were dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the ether was evaporated under reduced pressure. The remaining oil crystallized. The product (0.14 g, 18%) was recrystallized from benzene–alcohol (1:1), mp 140–142° (lit.[12] mp 144–145°).

The ^{18}O-labeled benzyl *p*-tolylsulfone was prepared as above from *p*-tolylmagnesium bromide (0.0018 mol, 2.0 ml) and the O^{18}-labeled (−)-menthyl phenylmethanesulfonate (0.43 g, 0.0014 mol). The sulfone was isolated by column chromatography (32 × 3 cm) on silica gel using purified chloroform as the eluent (0.067 g, 15%), mp 143–145°.

Removal of (−)-Menthol from Benzyl *p*-Tolylsulfone. (−)-Menthol (9.2 mg, 0.059 mmol) and unlabeled benzyl *p*-tolylsulfone (49 mg, 0.20 mmol) were dissolved in chloroform. After removal of the chloroform, (−)-menthol was removed from the mixture by two 20-ml extractions with boiling petroleum ether (bp 30–65°). The remaining benzyl *p*-tolylsulfone showed no optical activity from 300 to 600 mμ. *e.g.*, α_{320} −0.0003 ± 0.0002° (*c* 1.5, chloroform, 0.1 dm).

Removal of Benzyl *p*-Tolylsulfoxide from Benzyl *p*-Tolylsulfone. (+)-Benzyl *p*-tolylsulfoxide (1.0 mg, 0.41 mmol), $[\alpha]_D$ +244° (lit.[8] $[\alpha]_D$ +252°, chloroform), unlabeled benzyl *p*-tolylsulfone (35 mg, 0.14 mmol), and sodium acetate (930 mg, 1.10 mmol) were dissolved in glacial acetic acid (4.5 ml), and the mixture was diluted with water (1.8 ml). After addition of a 20% solution of titanium(III) chloride (1.80 mmol, 1.0 ml), the reaction mixture was heated (hot water bath) for 3 hr at 70°. The reaction mixture was cooled to room temperature and extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the chloroform was removed under reduced pressure. The residue was washed several times with petroleum ether (bp 35–60°) to remove benzyl *p*-tolylsulfide. The product (0.015 g, 43%) was obtained as white crystals (mp 143–145°) which exhibited no dextrorotation from 600 to 300 mμ (*c* 1.5, chloroform).

Purification of Benzyl *p*-Tolylsulfone-^{16}O,^{18}O. The ^{18}O-labeled sulfone (37.8 mg, 0.153 mmol) was boiled several times in fresh portions of petroleum ether as described above. The recovered sulfone (29.6 mg, 0.120 mmol) was treated twice with titanium(III) chloride as above followed by several more extractions with petroleum ether. After recrystallization from absolute alcohol, the final product (7.3 mg), mp 141–143°, gave a negative plain ORD curve from 340 to 280 mμ (Figure 1) (*c* 0.73, chloroform), $[\alpha]_{340}$ −0.14, $[\alpha]_{320}$ −0.41, $[\alpha]_{300}$ −1.64, $[\alpha]_{280}$ −6.2.

Purification of Unlabeled Benzyl *p*-Tolylsulfone. A sample of benzyl *p*-tolylsulfone was synthesized from unlabeled (−)-menthyl phenylmethanesulfonate which had been prepared from (−)-menthol and phenylmethanesulfonyl chloride. Upon isolation by chromatography on silica followed by extraction with petroleum ether as described above it showed no optical activity from 400 to 300 mμ.

Acknowledgments. The authors are deeply appreciative of Professor C. J. M. Stirling's help in providing us with his remaining sample of ^{18}O-labeled sulfone.

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(12) R. Otto, *Chem. Ber.*, **13**, 1272 (1880).