Synthesis and Stereochemistry of Optically Active [^{16}O,^{18}O]Sulphones

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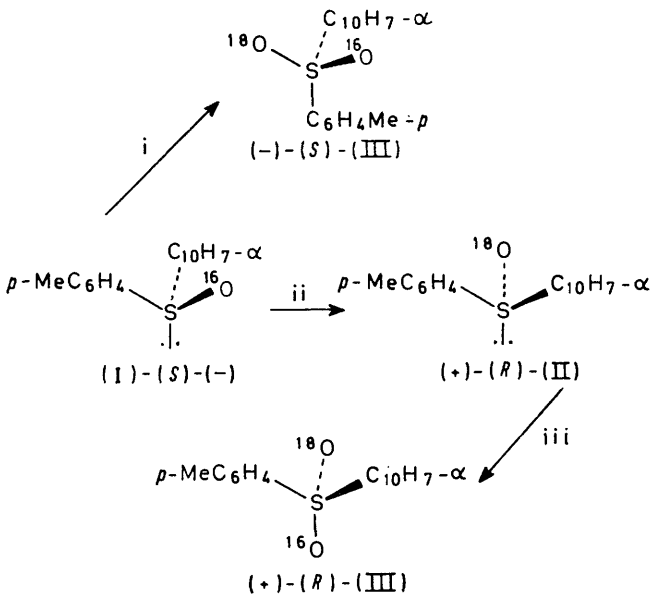
Two new syntheses of optically active [^{16}O,^{18}O]sulphones are reported. One uses reactions of known stereochemical course, thus allowing the determination of the absolute configuration of [^{16}O,^{18}O]sulphones. The other, oxidation of sulphoxides by (dichloroiodo)benzene, proceeds *via* nucleophilic attack at a tetraco-ordinate hexavalent sulphur atom and involves overall inversion of configuration.

ONLY one example of optical activity due to dissymmetry of an atom bonded to two isotopes of oxygen has hitherto been reported.[1,2] (−)-Benzyl *p*-tolyl [^{16}O,^{18}O]sulphone has been obtained [1] by oxidation of (+)-benzyl *p*-tolyl [^{16}O]sulphoxide with [$^{18}O_2$]peracetic acid, and also [2] by oxidation of (−)-menthyl phenylmethanesulphinate with potassium [$^{18}O_4$]permanganate to the corresponding [^{18}O]sulphonate followed by treatment with *p*-tolylmagnesium bromide. Since oxidations with peroxyacids [3] and with permanganate [2] should involve retention of configuration at the sulphur atom, the (*S*)-configuration was tentatively assigned [1,2] to the [^{18}O]sulphone. We report two new syntheses of optically active [^{16}O,^{18}O]-sulphones (Schemes 1 and 2). One involves reactions of known stereochemical course, so that the absolute configuration can be assigned to the [^{16}O,^{18}O]sulphones and the stereochemistry of the oxidation of sulphoxides by (dichloroiodo)benzene can be defined.

Diaryl sulphoxides react with (dichloroiodo)benzene

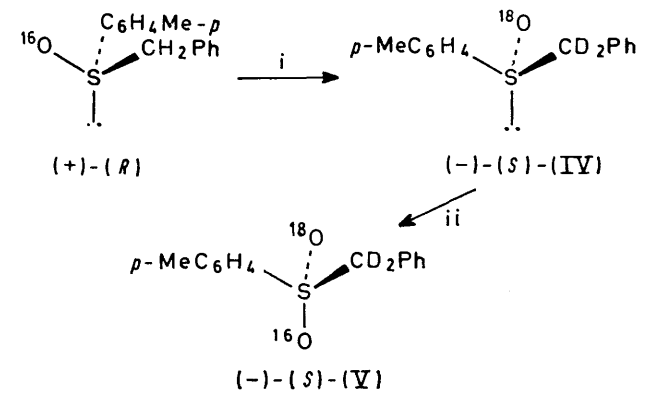
[1] C. J. M. Stirling, *J. Chem. Soc.*, 1963, 5741.
[2] M. A. Sabol and K. K. Andersen, *J. Amer. Chem. Soc.*, 1969, **91**, 3603.
[3] For a review see F. Montanari, M. Cinquini, and U. Folli, *Mechanisms of the Reactions of Sulphur Compounds*, 1968, **3**, 121.

in aqueous pyridine to give the corresponding sulphones.[4] The reaction is slowed down or prevented by the presence



SCHEME 1

Reagents: i, $PhICl_2$–$H_2{}^{18}O$–$AgNO_3$; ii, $Et_3O^+BF_4^-$ and then $Na^{18}OD$–$D_2{}^{18}O$–dioxan; iii, *m*-$ClC_6H_4{\cdot}CO_3H$.



SCHEME 2

Reagents: i, $EtO_3^+BF_4^-$,$Na^{18}OD$; ii, *m*-$ClC_6H_4{\cdot}CO_3H$.

of electron-withdrawing groups and by steric hindrance: while diphenyl and bis-(4-methoxyphenyl) sulphoxides afford a quantitative yield of the corresponding sulphone after 6 h at room temperature, 2,4-dinitrophenyl sulphoxide is recovered unchanged after 2 days reaction under the same conditions.[4]

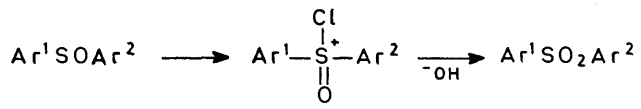
It was possible, in principle, to obtain optically active [^{16}O,^{18}O]sulphones from optically active sulphoxides, working with [^{18}O]-enriched water. However, oxidation of (−)-α-naphthyl *p*-tolyl sulphoxide (I) was slow, and the recovered sulphoxide was optically inactive. To prevent racemization, probably due to chloride ions,[5] the oxidation was carried out in the presence of silver(I) nitrate. Then the reaction was much faster and the recovered sulphoxide maintained its optical purity. By working with 92% [^{18}O]-enriched water, the optically active [^{16}O,^{18}O]sulphone (III) was obtained, 75% isotopically pure. To establish the stereochemical course of the reaction, we prepared the same sulphone *via* the ethoxysulphonium fluoroborate (see Scheme 1).

Alkylation of (−)-α-naphthyl *p*-tolyl [^{16}O]sulphoxide (I) followed by hydrolysis afforded the (+)-[^{18}O]-sulphoxide (II), which on oxidation gave the (+)-[^{16}O,^{18}O]sulphone (III), 83% isotopically pure (see Scheme 1). Unlike the first pathway, which is limited chiefly to the synthesis of diaryl sulphones, the second synthesis seems to be of wider applicability. Starting from (+)-*R*-benzyl *p*-tolyl [^{16}O]sulphoxide the (−)-αα-dideuteriobenzyl [^{16}O,^{18}O]sulphone (V) (83% isotopically pure) was obtained (see Scheme 2). Hydrolysis of the intermediate ethoxysulphonium fluoroborate is accompanied by H–D exchange of the benzylic protons to give the dideuterio-compound (IV). However, with short reaction times only hydrolysis and no exchange occurred.

In order to verify the absence of optically active impurities, the optically active sulphones were mixed with optically active sulphoxides. From the mixtures, purified by column chromatography, the [^{16}O,^{18}O]sulphones were recovered with no changes in the sign and no substantial variations in the values of specific rotations.

Hydrolysis of ethoxysulphonium salts is known to occur with inversion.[6] The (−)-(*S*) absolute configuration has been previously attributed [7] to (V). Assuming that oxidation of sulphoxides by peroxyacids proceeds with retention of configuration at the sulphur atom,[3] and knowing the (−)-(*S*) absolute configuration previously attributed to the sulphoxide (I),[7] the (−)-(*S*) and (+)-(*R*) configurations are assigned to sulphones (V) and (III), respectively. This tallies with the absolute configuration previously attributed to (−)-benzyl *p*-tolyl [^{16}O,^{18}O]sulphone.[1,2] Since oxidation of the (−)-(*S*)-sulphoxide (I) by (dichloroiodo)benzene in the presence of [^{18}O]-enriched water and silver(I) nitrate yielded the (−)-(*S*)-sulphone (III) (see Scheme 1), it must proceed with overall inversion.

(Dichloroiodo)benzene acts as a source of chlorine cations (Cl^+) in the oxidation of sulphides to sulphoxides [8]



SCHEME 3

and in the α-chlorination of sulphoxides.[9] It seems likely that the reaction (I) ⟶ (III) involves a *S*-

[4] G. Barbieri, M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc.* (*C*), 1968, 659.

[5] (*a*) K. Mislow, T. Simmons, J. T. Melillo, and A. L. Ternay, *J. Amer. Chem. Soc.*, 1964, **86**, 1452; (*b*) D. Landini, G. Modena, F. Montanari, and G. Scorrano, *ibid.*, 1970, **92**, 7168.

[6] C. R. Johnson and D. McCants, *J. Amer. Chem. Soc.*, 1965, **87**, 5404.

[7] K. K. Andersen, W. Gaffield, E. Papanikolau, J. W. Foley, and R. I. Perkins, *J. Amer. Chem. Soc.*, 1964, **86**, 5637.

[8] M. Cinquini, S. Colonna, and D. Landini, *Boll. sci. Fac. Chim. Ind., Bologna*, 1969, **27**, 211.

[9] M. Cinquini, S. Colonna, and D. Landini, *J.C.S. Perkin II*, 1972, 296.

chlorosulphoxonium intermediate (VI), which is converted into the sulphone by base (see Scheme 3). Since the formation of the cation (VI) should involve retention of configuration, as normally found in electrophilic reactions at sulphur, nucleophilic attack at the tetraco-ordinate hexavalent sulphur in (VI) should occur with inversion of configuration.

EXPERIMENTAL

Optical rotations were measured on a Cary model 60 recording spectropolarimeter and/or with a Perkin-Elmer 141 polarimeter. Mass spectra were recorded with a RMU Itachi 6D spectrometer.

Oxidation of (−)-α-*Naphthyl* p-*Tolyl Sulphoxide* (I) *by* (*Dichloroiodo*)*benzene*.—(*a*) A solution of (dichloroiodo)-benzene (0·55 g, 2 mmol) in anhydrous pyridine (10 ml) was added to a stirred solution of the (−)-sulphoxide (I) {m.p. 137°, $[\alpha]_D^{25}$ −399° (*c* 1, acetone), 96% optically pure (based on the highest reported value [7])} (0·54 g, 2 mmol) and water (0·25 ml) in anhydrous pyridine (5 ml) at −40°. The mixture was kept at −40° for 1 h and then at room temperature for 2 days. The solution was diluted with chloroform (50 ml), washed with cold aqueous sulphuric acid, and dried (Na_2SO_4). Evaporation gave the product, which was purified by column chromatography (silica; ether–light petroleum 1 : 1 v/v). The product was a mixture of α-naphthyl *p*-tolyl sulphone (III) (0·4 g, 70%), m.p. 122—123° (lit.,[10] m.p. 122°) and optically inactive sulphoxide (I), m.p. 108° (from cyclohexane) (Found: C, 76·45; H, 5·25. $C_{17}H_{14}OS$ requires C, 76·65; H, 5·3%).

(*b*) The reaction was carried out in the presence of silver(I) nitrate (0·81 g, 4·8 mmol) at −40° for 1 h and then at room temperature for 30 min to give the sulphone (III) (0·39 g, 69%), m.p. 122—123° and the (+)-sulphoxide (I) (0·12 g), m.p. 137°, $[\alpha]_D^{25}$ −399° (*c* 1, acetone) {lit.,[7] m.p. 136—137°, $[\alpha]_D^{25}$ −414 (*c* 1, acetone)}.

(*c*) The oxidation with [^{18}O]-enriched water (isotopic content 92%) in the presence of silver(I) nitrate was carried out at −40° for 1 h and at room temperature for 1 h. The crude mixture was purified twice by column chromatography (silica; ether–light petroleum, 1 : 1 v/v) to give (−)-α-naphthyl *p*-tolyl [^{16}O,^{18}O]sulphone (III) (0·42 g, 74%), 75% isotopically pure (mass spec.), m.p. 123—124° (from methanol), $[\phi]_{400}$ −0·41°, $[\phi]_{380}$ −0·46°, $[\phi]_{360}$ −0·60°, $[\phi]_{350}$ −0·75° (*c* 7·1, chloroform), plain o.r.d. curve, and the (−)-sulphoxide (I) (0·06 g), $[\alpha]_D^{25}$ −380° (*c* 1, acetone).

To check the reliability of the specific rotations, the (−)-[^{16}O,^{18}O]sulphone (III) (76·7 mg) was mixed with (+)-α-naphthyl *p*-tolyl [^{18}O]sulphoxide (II) (7·8 mg), {$[\alpha]_D^{25}$ +380°, $[\phi]_{365}$ +1979° (*c* 1, acetone)} and then separated by repeated column chromatography to give the [^{16}O,^{18}O]sulphone (III) (74 mg), $[\phi]_{350}$ −0·96 ± 0·11°, $[\phi]_{340}$ −0·93 ± 0·12° (*c* 2·5, chloroform). The presence of a 1% impurity of sulphoxide in an inactive sulphone should give $[\alpha]_{365}$ +1·98°.

In another test, optically inactive sulphone (III) (83·8 mg) was mixed with the (−)-sulphoxide (I) (24·2 mg), {$[\alpha]_D^{25}$ −405°, $[\phi]_{365}$ −2109° (*c* 1, acetone)}. Usual work-up gave the sulphone (III) (79·0 mg), $[\phi]_{350}$ −0·04 ± 0·04°, $[\phi]_{340}$ −0·05 ± 0·05° (*c* 7, chloroform). (It was noted that in some runs the base line of the instrument moved, causing errors, although not in sign, in the magnitude of rotation.

(+)-α-*Naphthyl* p-*Tolyl* [^{18}O]*Sulphoxide* (II).—The [^{16}O]-sulphoxide (I) {$[\alpha]_D^{25}$ −399° (*c* 1, acetone)} was converted into its ethoxysulphonium fluoroborate by the method of Johnson *et al.*[6] over 2 days. The resulting crude oil was washed several times with dry ether and benzene, and used without further purification. Hydrolysis with aqueous sodium hydroxide [6] gave the [^{16}O]sulphoxide (+)-(I) (80%), m.p. 136°, $[\alpha]_D^{25}$ +387° (*c* 1, acetone). To prepare the [^{18}O]sulphoxide (II), the foregoing ethoxysulphonium salt [from sulphoxide (I) (0·67 g, 2·5 mmol)] was hydrolysed in dioxan (6 ml) with sodium [^{18}O]deuterioxide [from $D_2{}^{18}O$ (0·6 ml) (92% ^{18}O) and sodium (0·115 g, 5 mmol)] at room temperature for 24 h. The mixture was diluted with chloroform (20 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the [^{18}O]sulphoxide (II) (0·47 g, 70%), m.p. 136° (from cyclohexane), $[\alpha]_D^{25}$ +380° (*c* 1, acetone), 80% ^{18}O (mass spec.).

(+)-α-*Naphthyl* p-*Tolyl* [^{16}O,^{18}O]*Sulphone* (III).—The [^{18}O]sulphoxide (II) (0·27 g) was oxidized to the corresponding [^{16}O,^{18}O]sulphone (III) with a slight excess of *m*-chloroperoxybenzoic acid in dichloromethane at room temperature for 24 h. The crude product was twice purified by column chromatography (silica; ether–light petroleum, 1 : 1 v/v) to give the pure [83% ^{18}O (mass spec.)] [^{16}O,^{18}O]sulphone (III) (0·22 g, 77%), m.p. 124° (from methanol), positive plain o.r.d. curve (*c* 9, chloroform), $[\phi]_{360}$ +0·16°, $[\phi]_{350}$ +0·27°. Further the (+)-[^{16}O^{18}O]sulphone (III) (144·3 mg) was mixed with the (−)-sulphoxide (I) (20·9 mg), $[\alpha]_D^{25}$ −405°, $[\phi]_{365}$ −2109° (*c* 1, acetone). Repeated purifications by column chromatography afforded the (+)-[^{16}O,^{18}O]sulphone (III) (143 mg), $[\phi]_{350}$ +0·59 ± 0·06°, $[\phi]_{340}$ +0·81 ± 0·05° (*c* 6, chloroform).

(−)-αα-*Dideuteriobenzyl* p-*Tolyl* [^{18}O]*Sulphoxide* (IV).—Benzyl *p*-tolyl sulphoxide was converted into its ethoxysulphonium fluoroborate (0·69 g, 2 mmol) {m.p. 115—116°, $[\alpha]_D^{25}$ +180° (*c* 1, acetone), $[\alpha]_D^{25}$ +205° (*c* 1, chloroform)} {lit.,[6] m.p. 115—117°, $[\alpha]_D^{25}$ +203° (chloroform)}, was hydrolysed as before to give αα-dideuteriobenzyl *p*-tolyl [^{18}O]sulphoxide (IV) (0·4 g, 88%), m.p. 166°, $[\alpha]_D^{25}$ −230° (*c* 1, acetone) {(+)-benzyl *p*-tolyl sulphoxide [1] has m.p. 169—170°, $[\alpha]_D^{25}$ +252° (acetone)}. The ^{1}H n.m.r. spectrum showed complete H–D exchange of the benzylic protons. With a shorter reaction time (20 min), hydrolysis occurred but no exchange was detectable, within experimental error.

(−)-αα-*Dideuteriobenzyl* p-*Tolyl* [^{16}O,^{18}O]*Sulphone* (V).—The foregoing [^{18}O]sulphoxide (IV) (0·23 g) was oxidized with a slight excess of *m*-chloroperoxybenzoic acid to give, after two purifications by column chromatography (silica; ether–light petroleum), the [^{16}O,^{18}O]sulphone (V) (83% ^{18}O mass spec.)] (0·2 g, 80%), m.p. 144° (lit.,[1] m.p .146—147°), negative plain o.r.d. curve (*c* 5, chloroform), $[\phi]_{360}$ −2·16°, $[\phi]_{350}$ −2·38°, $[\phi]_{340}$ −2·66°. To test the purity, the [^{16}O,^{18}O]sulphone (V) (0·13 g) was mixed with optically active (−)-αα-dideuteriobenzyl *p*-tolyl [^{18}O]sulphoxide (IV) (0·05 g), $[\alpha]_D^{25}$ −230° (*c* 1, acetone). Usual work-up afforded the sulphone (V) (0·11 g), $[\phi]_{365}$ −2·2° (*c* 5, chloroform). Also, optically inactive benzyl *p*-tolyl [^{16}O,^{18}O]-sulphone (0·13 g; m.p. 144°) was mixed with (+)-benzyl *p*-tolyl [^{16}O]sulphoxide (0·05 g; m.p. 169°), $[\alpha]_D^{25}$ +250° (*c* 1, acetone). The recovered benzyl *p*-tolyl [^{16}O,^{18}O]-sulphone (0·10 g) did not show any optical activity at 365 nm.

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[10] H. Meyer, *Annalen*, 1923, **433**, 327.