Stereochemistry of Intramolecular Homolytic Substitution at the Sulphur Atom of a Chiral Sulphoxide

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The formation of the cyclic sulphoxide (*R*)-(**6**) by treatment of the bromoarene (*R*)-(**2**) with tributylstannane indicates that intramolecular homolytic substitution at the sulphur centre of the sulphoxide group proceeds with strict inversion of configuration.

Heterocyclic ring formation by intramolecular homolytic substitution (S_Hi) at the sulphur atom in sulphides[1,2] and in sulphoxides[3] has been previously described. The simplest mechanism consistent with the data involves back-side attack with concerted displacement of the leaving group,[3] but existing experimental evidence unambiguously precludes neither a concerted front-side displacement nor the intervention of an intermediate in which the sulphur atom has increased its co-ordination number.[3,4] In an attempt to distinguish between these mechanistic possibilities we have now examined the behaviour of suitably constituted systems containing a chiral sulphoxide group.

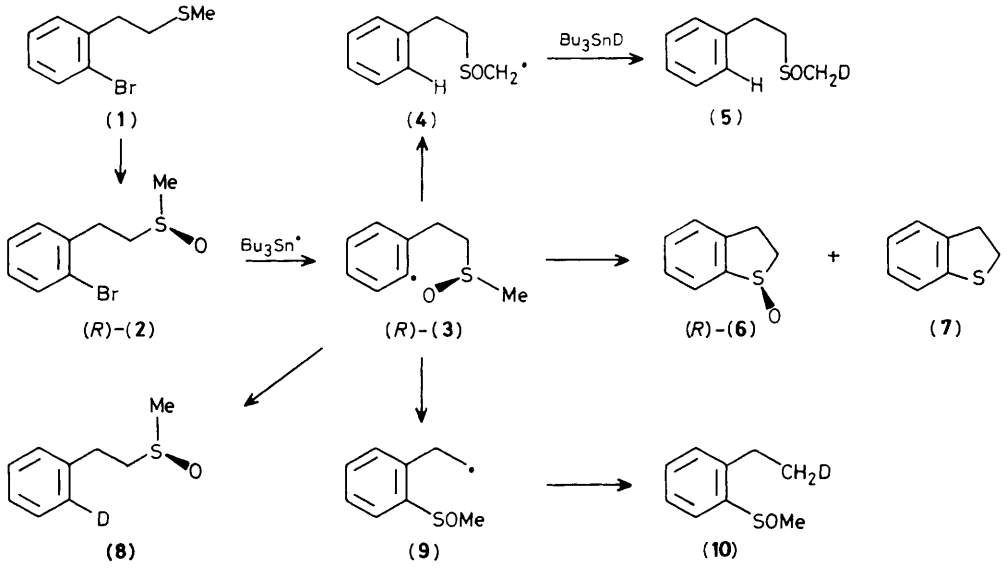
Enantiomeric sulphoxides† were prepared by asymmetric oxidation of the sulphide (**1**), and their stereochemical integrity was examined by ^{1}H n.m.r. spectroscopy (400 MHz) in the presence of the new chiral shift reagent (−)-*N*-3,5-dinitrobenzoyl-α-phenylethylamine.[5] Thus, treatment of (**1**) with homogeneous Sharpless reagent[6] prepared from (*R,R*)-diethyl tartrate gave the sulphoxide (*R*)-(**2**) (58%), m.p. 58—61 °C, $[\alpha]_D^{20}$ −64° (*c* 3.8, acetone), enantiomeric excess (e.e.) ≥96%, assignment of configuration to which depends upon analogy with the established stereochemical course of closely related oxidations.[6] The (*S*)-enantiomer, similarly prepared in 50% yield, had m.p. 55—61 °C, $[\alpha]_D^{20}$ +68° (*c* 0.7, acetone), e.e. ≥96%. Asymmetric oxidation of 2,3-dihydrobenzo[*b*]thiophene (**7**) gave an authentic sample (84%) of one enantiomer (*R*)-(**6**) of the expected cyclisation product,[7] b.p. *ca.* 100 °C/0.05 mm (Kugelrohr), $[\alpha]_D^{20}$ −254° (*c* 2.3, acetone), e.e. ≥94%.

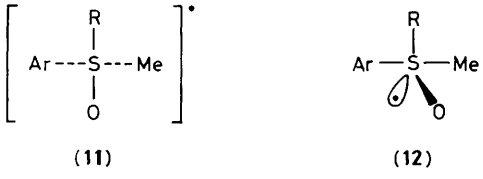
Treatment of the sulphoxide (*R*)-(**2**) with a trace of azobisisobutyronitrile and tributyltin deuteride (1.2 molar equiv., 0.03 M) in boiling benzene for 5 h afforded two cyclised products, the sulphide (**7**) (16%) and the sulphoxide (*R*)-(**6**) (74%), $[\alpha]_D^{20}$ −270° (*c* 3.3, acetone), e.e. ≥98%, which were separated by chromatography. The (*S*)-enantiomer‡ of the same starting material when heated with tributyltin deuteride under identical conditions afforded the sulphide (**7**) (14%) and 2,3-dihydrobenzothiophene 1-oxide as its (*S*)-enantiomer (75%), $[\alpha]_D^{20}$ +263 (*c* 3.3, acetone), e.e. ≥97%.

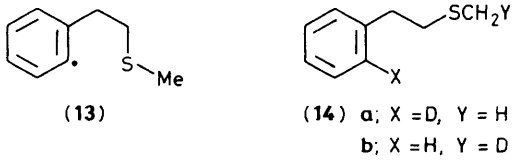
The foregoing experimental results support a number of mechanistic conclusions. First, the complete absence from the reaction mixtures of either enantiomer of the sulphoxide (**10**) indicates that *endo* substitution [*e.g.* (*R*)-(**3**) → (**9**)] does not occur. Conversely the high yields of the cyclised products (**6**) and (**7**) indicate that the *exo* ring closures [*e.g.* (*R*)-(**3**) → (*R*)-(**6**)] are highly efficient and proceed with *complete*

† Satisfactory spectral and microanalytical data were obtained for all new compounds.

‡ *Note added in proof:* The assignment of configuration has now been confirmed by *X*-ray crystallography of (*S*)-(**2**).







inversion of configuration.§ We conclude that the mechanism involves back-side attack, possibly by interaction of the SOMO σ orbital of the aryl radical with the S–Me σ* orbital,[8] and proceeds either through a colinear transition structure (**11**) or through a trigonal bipyramidal intermediate (**12**) in which the entering and leaving groups occupy apical positions.[4] In the latter case, the observation of strict inversion of configuration demands that the rate of pseudorotation of the intermediate (**12**) be slow with respect to the rate of departure of the leaving group.

The failure of the reaction to afford either of the open-chain products (**5**) or (**8**) indicates that under the reaction conditions used neither direct reduction (*R*)-(**3**) → (**8**) nor 1,6-hydrogen atom transfer (*R*)-(**3**) → (**4**) is sufficiently fast to compete with ring formation. This contrasts with the behaviour of some sulphide containing aryl radicals in which intramolecular hydrogen-atom transfer is very rapid.[1] Since the direct reduction process (*R*)-(**3**) → (**8**) probably has a rate constant[9] of about 4×10^8 s^{-1} at 80 °C, and the limit of detectability of (**8**) is 2% or less, we calculate that the rate constant for ring closure must be at least 3×10^8 s^{-1}.

For comparison we have conducted comparative experiments on the sulphide (**1**). Treatment of (**1**) with tributyltin deuteride in benzene (0.03 M) as described above gave a mixture containing the cyclised product (**7**) (84%) and two open chain deuteriated compounds (**14a**) (10%) and (**14b**) (6%) from which data it can be calculated that the rate constant for ring closure of the radical (**13**) is about 5×10^7 s^{-1} at 80 °C while that for 1,6-hydrogen atom transfer is about 4×10^6 s^{-1}. Experiments are now in hand to determine whether the more rapid cyclisation of the sulphoxide radical (*R*)-(**3**) by comparison with the corresponding sulphide (**13**) is but one example of a general phenomenon.

Finally, we conclude that the cyclic sulphide (**7**) probably arises by reduction of the sulphoxide (**6**).[10] The same transformation can be accomplished in high yield by heating its (*S*)-enantiomer with tributylstannane in benzene.

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§ The displacement reaction results in a change in substituent priority; hence the reaction (*R*)-(**3**) → (*R*)-(**6**) represents inversion of configuration.

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