Concerning the Absolute Configuration of Proton Exchange at a Prochiral Centre in Sulphoxides

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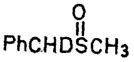
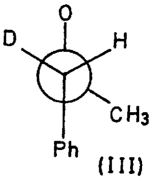
Summary Deuterium exchange of the kinetically more labile proton in (*S*)-benzyl methyl sulphoxide yields the (*R*) configuration at the benzylic carbon atom, an observation opposite to what others have previously reported.

THE phenomenon of kinetic nonequivalence in the proton exchange at the prochiral centre of benzyl methyl sulphoxide (I) has recently received considerable attention.[1-3] It was shown that the chemically and magnetically distinct benzylic protons of this molecule exhibit different rates of base-catalysed proton exchange, such that it was possible to isolate a monodeuterio-species (II).[1] Furthermore, in a sample of (I) of known chirality (*S*) it was demonstrated that the kinetically more labile proton exchanges with deuterium to produce the (*S*) configuration at carbon,[2] illustrated by Newman projection (III), and subsequently extensive LCAO–MO–SCF calculations were undertaken and found to provide theoretical support for this experimental configurational relationship.[3] More recently still the chlorination at this prochiral centre has been shown to involve the diastereotopic proton,[4] the earlier configurational results[2,3] being used to define the steric course of this process. Since one of the quantum-mechanical findings[3] was that the carbanion intermediate for exchange was pyramidal, a result we felt to be unusual for a benzylic anion, we have re-examined the above work and have discovered that the earlier configurational relationships are in error. Thus a sample of (*R*)-(−)-α-deuteriobenzyl alcohol (IV), $[\alpha]_D^{22}$ −0·748 ± 0·002°† (neat), obtained as described by Streitwieser[5] was transformed, *via* the tosylate, into the (*S*)-(+)-methyl sulphide (V), $[\alpha]_D^{20}$ + 0·73 ± 0·02° (*c* 12 in EtOH) and thence into the (*S*)-(−)-sulphone (VI), $[\alpha]_D^{25}$ −0·60 ± 0·04° (*c* 6 in $CHCl_3$), m.p. 127·5—128·0°. We have confirmed the observation[2] that the enantiomorph, $[\alpha]_D^{25}$ +0·83 ± 0·04° (*c* 4 in $CHCl_3$) m.p. 127·5—128·0°, of this sulphone (VI) is obtained by exchange of (*S*)-(+)-benzyl methyl sulphoxide to the extent of uptake of one deuterium, followed by oxidation to the sulphone. The configuration of the benzylic carbon in the exchanged (*S*)-(+)-sulphoxide must therefore be *R*, as is expressed by the Newman projection (VII). It should be noted that since exchange with inversion causes interchange of the diastereotopic substituents at the benzylic centre, only exchange with retention of configuration would give this stereochemically discrete product of the (*R*) configuration. Further evidence was obtained when the enantiomorph of the sulphide (V) was formed by reduction of the sulphoxide (II) with triphenylphosphine,[6] giving $[\alpha]_D^{25}$ −1·12 ±0·02° (*c* 18 in EtOH).

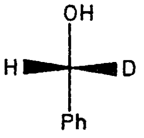


$PhCHD\overset{O}{\overset{\|}{S}}CH_3$

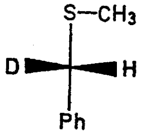
(II)



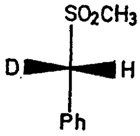
(III)



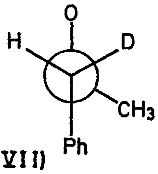
(IV)



(V)



(VI)



(VII)

This result is in contradiction to that earlier reported on the basis of experiment[2] and justified theoretically.[3] Because of this we sought to discover the experimental source of the previous error. It is evident that all of the earlier assignments[2] rested on the positive rotation of the alleged (*S*)-(+)-α-deuteriobenzyl alcohol, obtained by reduction of benzaldehyde with (−)-di-isopinocampheyldeuterioborane[7] derived from (+)-pinene. This rotation is reported both as $[\alpha]_D^{22}$ +0·33° [7] (*c* 10 in $CHCl_3$) and $[\alpha]_D$ +0·47° [2] (*c* 10 in $CHCl_3$). Repetition of this preparation using (+)-α-pinene, $[\alpha]_D^{25}$ +50·5° (*c* 2 in EtOH), gave in fact (*R*)-(−)-α-deuteriobenzyl alcohol (IV), $[\alpha]_D^{25}$ −0·21 ± 0·02° (*c* 20 in $CHCl_3$), purified as earlier described. Further purification by preparative g.l.c. and crystallization of the 3,5-dinitrobenzoate gave (*R*)-(−)-α-deuteriobenzyl alcohol (IV), $[\alpha]_D^{25}$ −0·20 ± 0·02° (*c* 14 in $CHCl_3$). To ensure that we were dealing with the alcohol of the same absolute configuration as was originally used,[2] we converted this (−)-alcohol (IV) into the (*S*)-(−)-sulphone (VI), $[\alpha]_D^{27}$ −0·27 ± 0·03° (*c* 7 in $CHCl_3$) m.p. 127·0—127·5°, which was the same as that obtained by the identical route for the supposed (*S*)-(+)-alcohol.[2] Finally, to avoid the high probability that some highly-rotating impurity was the source of rotation of the alcohol produced by the borane reduction, we repeated the reaction with (+)-pinene, but used α-deuteriobenzaldehyde with sodium borohydride, and obtained (*S*)-(+)-α-deuteriobenzyl alcohol, $[\alpha]_D^{27}$ +0·23 ±0·03° (*c* 12 in $CHCl_3$), purified through the hydrogen phthalate. As the strongly rotatory impurities from the reagent would be expected to have the same sign of rotation in both reductions (deuterium contribution is small) then the observation of oppositely rotatory product signifies that its rotation is true. This may be a useful general procedure in asymmetric syntheses where products have very low rotations relative to reagents. The steric course of reduction of benzaldehyde by di-isopinocampheyldeuterioborane is thus in complete accord with recent results in the aliphatic series.[8]

Therefore the exchange of the kinetically more labile benzylic proton in (*S*)-benzyl methyl sulphoxide yields the (*R*) configuration (VII). It should be made clear that this result, as did the original work, rests upon the absolute configurational assignment of α-deuteriobenzyl alcohol, which is based on the chemical correlations of Streitwieser[9] and Mosher,[10] the steric course of enzymic reduction of aldehydes with yeast,[10,11] and the Conformational Asymmetry Rule of Brewster.[12]

These results exemplify the need for great caution in work with optically active materials of small rotations in asymmetric syntheses from strongly rotatory precursors.

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† All optical rotations were measured on a Perkin-Elmer P22 Spectropolarimeter at a series of wavelengths from 589—300 nm. All solid materials were recrystallized to constant m.p. and rotation.

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