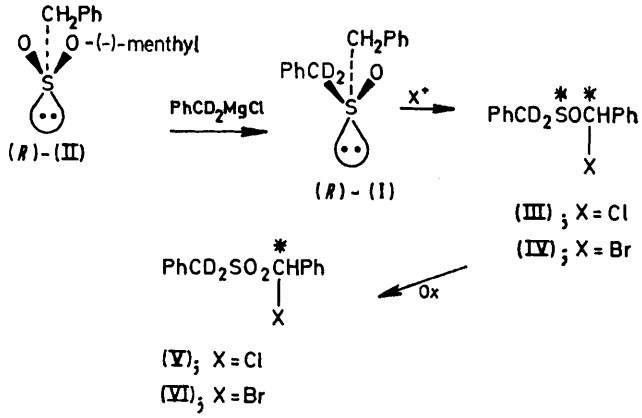
Asymmetric Induction by Isotopic Dissymmetry in [αα-$^2H_2$]Dibenzyl Sulphoxides

By MAURO CINQUINI* and STEFANO COLONNA
(*Centro C.N.R. e Istituto di Chimica Industriale dell'Università, Via C. Golgi* 19, 20133 *Milano, Italy*)

Summary Reaction of (*R*)-(+)-[αα-$^2H_2$]dibenzyl sulphoxide with $PhICl_2$ or bromine in pyridine to afford preferentially one of the four possible diastereoisomeric α-halogenosulphoxides is highly stereoselective; the corresponding α-halogenosulphones are optically active, thus indicating that asymmetric induction is operating.

EXAMPLES of chirality due to isotopic dissymmetry are known for hydrogen isotopes[1] and to a less extent for oxygen[2] and carbon[2] isotopes. Although kinetic resolution due to a steric isotope effect has been reported,[3] to the best of our knowledge asymmetric induction promoted by an isotopically dissymmetric centre has never been achieved. A suitable reaction should involve an high degree of stereoselectivity and possibly a strong primary isotope effect in order to be regioselective. These requirements are met in the α-halogenation with (dichloroiodo)benzene[4] and bromine[4] in pyridine of (*R*)-(+)-[αα-$^2H_2$]dibenzyl sulphoxide (I).

Compound (I) was obtained in 65% yield by reaction at −40° of [αα-$^2H_2$]benzylmagnesium chloride[5] with (−)-menthyl (*R*)-(+)-toluene-ω-sulphinate† (II) and purified by repeated column chromatography on silica in Et_2O–light petroleum and crystallization from EtOH–H_2O. It had $[\alpha]_D^{25}$ +2·19° (*c* 7, $CHCl_3$), m.p. 128°, isotopic purity 93% (by mass spec.). α-Chlorination of (*R*)-(+)-(I) afforded in 60% yield a single diastereoisomeric α-chlorobenzyl [α′α′-$^2H_2$]-benzyl sulphoxide (III) together with a single diastereoisomeric α-chloro[^{2}H]benzyl benzyl sulphoxide (VII) in 9:1 ratio.‡ The reaction product had m.p. 114—115°, $[\alpha]_D^{25}$ + 19·6°, $[\alpha]_{436}^{25}$ + 34·5°, $[\alpha]_{365}^{25}$ + 45·9° (*c* 3, $CHCl_3$), after column chromatography (SiO_2, Et_2O–light petroleum). On oxidation with *m*-chloroperoxybenzoic acid it afforded in 90% yield the corresponding sulphone (V), m.p. 120·5°, $[\alpha]_D^{25}$ + 12·3°, $[\alpha]_{436}^{25}$ + 14·5° (*c* 3, $CHCl_3$).



α Bromination with bromine in pyridine of (*R*)-(+)-(I) gave α-bromobenzyl [α′α′-$^2H_2$]benzyl sulphoxide (IV), a mixture of diastereoisomers in 8:1 ratio. With reaction times of 12 and 48 h the yields were 15 and 45%, respectively, $[\alpha]_D^{25}$ − 32·5° and −22·1° (*c* 2, $CHCl_3$), with 60 and 40%, respectively, recovery of unchanged sulphoxide. No products derived from attack at the deuteriated carbon of (I) were detected. The results show that in the bromination a longer reaction time increased the yield, but enhanced racemization within a single diastereoisomeric species. In other words, the different optical activity of (IV) is due to a different ratio of enantiomers. Oxidation with *m*-chloroperoxybenzoic acid of the mixtures (IV), $[\alpha]_D^{25}$ − 32·5° and −22·1° (*c* 2, $CHCl_3$), afforded the corresponding α-bromobenzyl [α′α′-$^2H_2$]benzyl sulphone (VI), m.p. 101—102° $[\alpha]_D^{25}$ − 23·6° (*c* 2, $CHCl_3$), and m.p. 102—103°, $[\alpha]_D^{25}$ − 15·6° (*c* 2, $CHCl_3$), respectively.

The experimental data clearly indicate that α-chlorination and α-bromination of (*R*)-(I) are both highly stereo- and regio-selective, stereoselectivity being more relevant in the former and regioselectivity in the latter reaction.

The sulphinyl group is unusual, with respect to other chiral groups, in carrying ligands which are very different from each other in their stereoelectronic properties (lone pair, oxygen, and only two alkyl or aryl groups).[9] From this is probably derived its ability to promote asymmetric induction, in particular in electrophilic reactions in benzylic systems.[9] In the α-halogenation of (*R*)-[αα-$^2H_2$]-dibenzyl sulphoxide (I) the strong primary isotope effect leads to a different reactivity of the two groups, $PhCH_2$ and $PhCD_2$, enantiotopic in all essential aspects. This is accompanied by a high stereoselectivity, which gives rise to preferential substitution of one of the two diastereotopic hydrogen (or deuterium) atoms. The net result is that one of the four possible diastereoisomeric α-halogeno-sulphoxides is preferentially formed. Apart from enzymatic processes, the reaction of (*R*)-(I) thus provides what we think to be the first example of an asymmetric induction by isotopic dissymmetry.

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† Compound (II) had optical purity > 91%;[2] the (*R*) configuration was assigned to (+)-(I) since displacement of menthol from the (*R*)-sulphinate (II) occurs with inversion of configuration.[6]

‡ The diastereoisomeric purity was checked by comparison of the ^{1}H n.m.r. spectrum in CCl_4 of (III) with those of the isotopically normal analogue[7] (VIII) and of its epimer (IX), the latter being obtained by inversion[8] of the sulphinyl group of (VIII).

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