Stereoselectivity of Prochiral Thioalkyl Groups in the Enzymatic Oxidation of Thioacetals by Fungi

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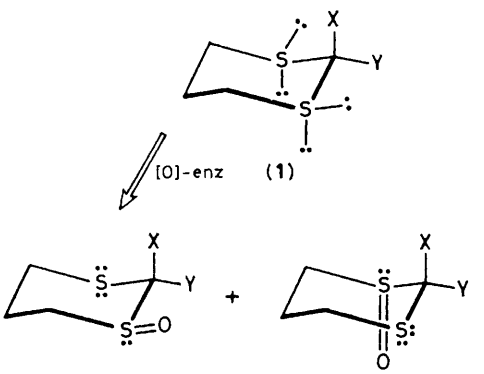
Enzymatic oxidation of 2-substituted 1,3-dithians in cultures of a *Helminthosporium* species shows a stereopreference for equatorial oxidation and for (1*S*)-monosulphoxide products.

Each sulphur atom of 1,3-dithian (**1a**) and its 2-alkyl- (**1b,c**) and 2,2′-dialkyl-derivatives (**1d,e**) bears both a *pro-R* and a *pro-S* lone pair of electrons, and the lone pair with a given prochirality has an equatorial orientation at one sulphur atom but an axial orientation at the other. Previous studies[1–3] have shown that the mono-oxygenase enzymes produced by fungi distinguish between a *pro-R* and a *pro-S* lone pair of electrons of a sulphur atom in the oxidation of (**1a**) and its analogues without a prochiral 2-carbon atom. A concomitant axial–equatorial enzymatic discrimination is reported here at *pro-R* and *pro-S* thioalkyl groups in an extension of the studies to 2-prochiral-1,3-dithians (**1b,c,d**).

The thioacetals (**1b—d**) were added individually as substrates to cultures of a *Helminthosporium* species (NRRL 4671) and the *trans*-monosulphoxide (**2**) and *cis*-monosulphoxide (**3**) products were separated and purified by column chromatography on silica gel, followed by preparative h.p.l.c.[4] (yields 35—65% overall from the substrate). In each case, the *trans*-monosulphoxide (**2b,c,d**) is found to be the major product (82—100%) (Table 1), showing the steric preference of the fungal mono-oxygenase enzyme(s) for the equatorial lone pairs of the corresponding 1,3-dithian (**1b,c,d**). The achiral oxidant $NaIO_4$ similarly differentiates between the diastereotopic lone pairs of the sulphur atoms in (**1b,c,d**), affording the corresponding *trans*-monosulphoxide (**2b,c,d**) as the major product (90—100%).

In order to evaluate the stereopreference of the enzymatic oxidation for the *pro-R* or *pro-S* thioalkyl groups, the (+)-(1*R*,2*R*)-*trans*-monosulphoxide (**2b**) (enantiomer) ($[\alpha]_D$ + 62°) and the (+)-(1*R*,2*S*)-*cis*-isomer (**3b**) (enantiomer)



a; X = H, Y = H
b; X = H, Y = Me
c; X = H, Y = Bu^t
d; X = Me, Y = Bu^t
e; X = Me, Y = Me

($[\alpha]_D$ + 201°) were synthesised by the 2-methylation of (+)-(1*R*)-1,3-dithian 1-oxide[5] (**2a**) ≡ (**3a**) (enantiomer) ($[\alpha]_D$ + 227°, EtOH). A comparison of the $[\alpha]_D$ rotations and the c.d. spectra of the synthetic (+)-(1*R*)-monosulphoxides with the corresponding values for the products of the enzymatic oxidation of (**1b**) in the cultures of the *Helminthosporium* species shows that the major metabolites are the (−)-(1*S*,2*S*)-

Table 1. Relative yield and $[\alpha]_D$ (EtOH) of the monosulphoxide metabolites (**2b,c,d**) and (**3b,c**) and the enantiomeric excess (e.e.) and configuration of the preferred enantiomer assigned from comparisons of the c.d. spectra.

Sulphoxide	Yield,[a] %	$[\alpha]_D$[b]/°	E.e.,[c] %	Configuration	λ/nm	$\Delta\epsilon$[d]
(**2b**)	86	−17	27	(1*S*, 2*S*)	235	−19.7
					203	+29.0
(**3b**)	14	−71.5	36	(1*S*, 2*R*)	231	−23.0
					202	+9.6
(**2c**)	82	−13	35	(1*S*, 2*S*)	237	−23.4
					203	+27.4
(**3c**)	18	+83	72	(1*S*, 2*R*)	245	−3.6
					215	−35.0
(**2d**)	100	0	0	racemic		

[a] Estimated by duplicate n.m.r. analyses of the product mixture (250 MHz, $CDCl_3$). [b] Obtained from product samples after isolation by preparative h.p.l.c. [c] Obtained by n.m.r. analysis (ref. 6) and duplicated by $[\alpha]_D$ comparisons. [d] The c.d. values refer to optically pure isomers in cyclohexane solution; comparison values obtained from synthesised enantiomers are, for the (−)-(1*S*)-isomers, $\Delta\epsilon_{233}$ −19.5, $\Delta\epsilon_{202}$ +13.5 (**2a**) ≡ (**3a**), and $\Delta\epsilon_{232}$ −25.6, $\Delta\epsilon_{215}$ +21.8 (**2e**) ≡ (**3e**), together with the values recorded for (**2b**) and (**3b**).

enantiomer (**2b**) and the (−)-(1*S*,2*R*)-enantiomer (**3b**), produced in an enantiomeric excess of 27% and 36%, respectively (Table 1). The same values for the enantiomeric excess of (**2b**) and (**3b**) were estimated by the n.m.r. method of Pirkle and coworkers,[6] using solutions in (−)-phenyl- or 1-(+)-9-anthryl-2,2,2-trifluoroethanol, diluted with $CDCl_3$, to distinguish the ^1H n.m.r. signals of the 2-alkyl groups in each enantiomer. The optical yields of the major metabolites (**2c**) and (**3c**) from (**1c**) were estimated by the n.m.r. method, and the respective (1*S*,2*S*) and (1*S*,2*R*) configurations were assigned by comparisons of the c.d. spectra (Table 1).

Only the *trans*-monosulphoxide (**2d**) in racemic form was isolated from the enzymatic oxidation of the thioacetal (**1d**), the most sterically crowded of the 1,3-dithians examined. In contrast, the less crowded thioacetal (**1c**), in which the bulk of the 2-t-butyl group is not buttressed by another alkyl group at the 2-carbon atom, as in (**1d**), gives the largest enantiomeric excess (72%) of the series investigated in the minor *cis*-monosulphoxide product (**3c**) from the enzymatic oxidation (Table 1). The lack of chiral discrimination in the enzymatic oxidation of (**1d**) does not arise from 2,2′-dialkyl substitution, since the thioacetal (**1e**) in cultures of the *Helminthosporium* species was oxidised to (**2e**) ≡ (**3e**), with a 35% enantiomeric excess of the (−)-(1*S*)-isomer, comparable to the optical yields of the (−)-(1*S*)-enantiomers of (**2b**) and (**3b**) from the corresponding oxidation of the thioacetal (**1b**) (Table 1).

The partial recovery of racemic monosulphoxides after their incubation with growing cultures of the *Helminthosporium* species eliminates the possibility of optical activity resulting from selective removal of one enantiomer during metabolism.

Overall, the product analyses suggest that the enzymatic oxidation of the thioacetals (**1b,c**) has a stereopreference of *ca.* 27—35% for equatorial oxidation of the *pro-S* thioalkyl group or *ca.* 36—72% for axial oxidation of the *pro-R* thioalkyl group. These results (and methods of stereochemical assignment) are of particular relevance in view of earlier work on other thioacetal sulphoxides which have also been produced under enzymatic control.[3,7]

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