Asymmetric Oxidation of Sulphides, catalysed by Chloroperoxidase

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Chloroperoxidase oxidation of sulphides affords the corresponding sulphoxides having the (*R*) absolute configuration in up to 92% enantiomeric excess (e.e.).

Chloroperoxidase is a heme protein that catalyses halonium cation transfer from halide/H_2O_2 and oxygen transfer from H_2O_2 to a wide variety of organic substrates.[1] It has recently been used in the oxidation of thioanisoles to the corresponding sulphoxides,[2—4] but surprisingly there is only one example of asymmetric synthesis of this kind reported in the literature[4] and this occurs in poor optical yield (12.7% e.e.). We wanted to ascertain if this enzyme exhibits broad substrate specificity, the degree of enantioselectivity in the transfer of oxygen to sulphur, and the steric course of the reaction.

p-Tolyl methyl sulphide was chosen as the model substrate since the stereocentre at sulphur is stable to pyramidal inversion. Preliminary results at pH 5 and 4 °C† indicated that Bu^{t}OOH is the oxidant of choice in view of the stereoselectivity (86% e.e.) and the higher chemical yield obtained. H_2O_2 gave lower enantioselectivity (37% e.e.); cumene hydroperoxide, iodosylbenzene, and trityl hydroperoxide afforded racemic or almost racemic sulphoxide. The optically active *p*-tolyl methyl sulphoxide always had the (+)-(*R*) absolute configuration.

In order to verify the generality of this type of asymmetric synthesis, we investigated the Bu^{t}OOH oxidation of other aryl alkyl sulphides and of dialkyl sulphides.† Reaction time, chemical yield, absolute configuration, and e.e. are reported in Table 1. The data show that *para*-substitution led to higher asymmetric induction and higher chemical yield than *ortho*-substitution, and that electronic and particularly steric effects appear to influence the outcome of the reaction. Alkyl substituents more demanding than the ethyl group led to the recovery of unchanged starting material after a very long reaction time. Chloroperoxidase gave asymmetric induction also with dialkyl sulphides. Particularly significant was the result with benzyl methyl sulphoxide (91% e.e.), since

† The sulphide (1 mmol) and the oxidant (2 mmol) were stirred at 4 °C in 50 ml of pH 5 buffer solution containing 1.6×10^{-5} mol. equiv. of chloroperoxidase; the crude products were purified by preparative layer chromatography.

Table 1. Chloroperoxidase catalysed oxidation of sulphides R_S–S–R_L[a] using Bu^{t}OOH.

R_L	Time/ days	% Yield	Absolute configuration	E.e. (%)[b]
p-Tolyl	8	60	(+)-(*R*)	86
o-Tolyl	10	27	(+)-(*R*)	19
p-ClC_6H_4	8	44	(+)-(*R*)	85
p-$O_2NC_6H_4$	4	7	(+)-(*R*)	39
Ph	8	100	(+)-(*R*)	76
p-$MeOC_6H_4$	8	70	(+)-(*R*)	92
o-$MeOC_6H_4$	9	33	(+)-(*R*)	25
2-Naphthyl	9	0	—	—
p-Tolyl[c]	10	40	(+)-(*R*)	30
$PhCH_2$	9	51	(−)-(*R*)	91
Bu^n	8	54	(−)-(*R*)	38

[a] R_S and R_L stand for the small and large group, respectively. R_s is Me unless otherwise noted. [b] Measured by the specific rotation of isolated sulphoxide with use of the maximum specific rotations given in ref. 8. [c] R_s = Et.

homolytic racemization is well known to occur readily for this sulphoxide.

In all cases examined the prevailing sulphoxide had the (*R*) absolute configuration. This stereochemical course can be rationalized on the basis of the electrophilic attack of sulphur by the oxidant from the less hindered side.

The same stereochemical outcome has been found in most of the enzymatic oxidations of sulphides with cytochrome P-450 from rabbit liver,[5] although they occur with lower stereoselectivity.

The asymmetric sulphoxidation by chloroperoxidase compares favourably with the same reaction performed with *Mortierella isabellina*, a fungine P-450 containing mono-oxygenase, which also leads to (*R*) sulphoxides as the prevailing enantiomer.[6] Very high enantiomeric excesses in the oxidation of sulphides are currently possible only by Kagan's chemical method.[7]

Received, 16th May 1988; Com. 8/01912F

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