Stereoselective Formation of Aromatic Sulphoxides by Oxidation of Sulphides and Sulphoxides in the Presence of Bovine Serum Albumin

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Summary The two-stage stereoselective oxidation of aromatic sulphides and sulphoxides in the presence of bovine serum albumin produced optically active sulphoxides in exceptionally high optical purity compared to those obtained by sulphide-oxidizing micro-organisms.

OPTICALLY active sulphoxides are formed in moderate or high optical purity when unsymmetric sulphides are treated under aerobic conditions with micro-organisms, *e.g.*, *Aspergillus niger*, *Rhizopus arrhizus*, and *Rhizopus stolonifer*. Sulphones are often obtained in appreciable yields as by-products. The appearance of optical activity in the sulphoxide may be accounted for by stereoselective oxidation of the sulphide to the sulphoxide, followed by preferential loss of one of the enantiomeric sulphoxides by further reaction leading to the sulphone. We have recently demonstrated a highly stereoselective oxidation of aromatic sulphides to sulphoxides by the use of bovine serum albumin (BSA), whose hydrophobic binding domain mimics the chiral environment of the enzyme active site in the above micro-organisms.[1] BSA can also induce a high stereoselectivity in kinetic resolution of racemic aromatic sulphoxides. We report here the first successful production of optically active aromatic sulphoxides in >90% optical purity directly from the sulphides using the same two-stage stereoselective oxidation as in microbial systems, see equation (1).

$$R^1SR^2 \xrightarrow[BSA]{[O]} R^1S(O)R^2 \xrightarrow[BSA]{[O]} R^1S(O)_2R^2 \qquad (1)$$

(**1**) (**2**)

In a typical experiment racemic isobutyl phenyl sulphoxide (**2c**) (0·25 mmol) was oxidized with 30% hydrogen peroxide (2·5 mmol) in a 0·05 M borate buffer solution (pH 9·2) containing BSA (Fraction-V, Armour) (0·083 mmol) at 25 °C. The sulphoxide left after partial oxidation was optically active and the optical purity increased as the reaction proceeded: *e.g.*, 33 and 69% optical purity for 50 and 75% conversions, respectively. Other racemic sulphoxides also exhibited kinetic resolution with a stereoselectivity of 1—21% at *ca.* 50% oxidation (Table).†

This BSA method showed a stereoselectivity comparable to that obtained by microbial oxidation (usually 0—45%).[2] It was also superior to previous kinetic resolution methods, using a chiral reducing[3] or oxidizing agent,[4] where the best optical purity of sulphoxide obtained was 6%. It should be noted that a *para*-methyl substituent in the aromatic sulphoxide influenced the oxidation rates of the two enantiomeric sulphoxides. Thus, in a racemic alkyl phenyl sulphoxide the *S* enantiomer was oxidized at a much faster

† When the oxidation of racemic sulphoxides was carried out in various solutions containing BSA in the range 0·015—0·1 mmol, the maximum optical purities of sulphoxides were obtained when *ca.* 1/3 mol. equiv. of BSA (0·076—0·083 mmol) was used. The stereoselective oxidation was also strongly affected by the pH value of the buffer solution used. At pH values >9 the best optical purities of sulphoxides were obtained.

TABLE. Stereoselective oxidation of the aromatic sulphides (**1**) and the racemic sulphoxides (**2**) with hydrogen peroxide in the presence of BSA.

	Aromatic sulphide (**1**) or sulphoxide (**2**)		Enantiomeric sulphoxides (**2**) produced by				
			Sulphide oxidation[a]			Kinetic resolution of racemic sulphoxide[b]	
	R^1	R^2	Isolated yield/%	Optical purity/%[c]	Configuration	Optical purity/%[c]	Configuration
a	Ph	Pr^i	78	62	*R*	18	*R*
b	Ph	Bu^n	82	65	*R*	16	*R*
c	Ph	Bu^i	90	65	*R*	33	*R*
d	Ph	Bu^t	65	45	*R*	5	*R*
e	Ph	$PhCH_2$	35[d]	71	*R*	21	*R*
f	C_6H_4Me-*p*	Pr^i	73	1	*R*	6	*S*
g	C_6H_4Me-*p*	Bu^n	79	16	*R*	4	*S*
h	C_6H_4Me-*p*	Bu^t	65	12	*R*	1	*S*
i	C_6H_4Me-*p*	$PhCH_2$	31[d]	73	*R*	17	*R*

[a] The sulphoxides were isolated pure by preparative silica gel t.l.c. and showed satisfactory spectral data. [b] At *ca.* 50% completion of oxidation. [c] The optical purities of sulphoxides were calculated using the values of optical rotations for the optically pure sulphoxides. [d] The formation yields of the sulphones were < 5% except for the oxidation of benzyl sulphides (**1e**) and (**1i**), where the oxidation did not stop at sulphoxide formation because of rapid over-oxidation. Accordingly, the optical purities of (**2e**) and (**2i**) in the Table involve the effect of kinetic resolution.

rate than the *R* enantiomer, leaving the *R*-enriched sulphoxide in moderate optical purity. However, when starting with a racemic alkyl *p*-tolyl sulphoxide slightly preferential loss of the *R* enantiomer gave the *S*-enriched sulphoxide in low optical purity.

A similar kinetic resolution was also involved during the oxidation of aromatic sulphides. When isopropyl phenyl sulphide (**1a**) (0·25 mmol) was oxidized with 5 mol. equiv. of 30% hydrogen peroxide (1·25 mmol) for 12 h under the same conditions as used in the kinetic resolution experiment,‡ the *R* sulphoxide (**2a**), 62% optical purity, was obtained in 78% yield. In this case the yield of sulphone was < 5%. Results for the oxidation of sulphides to the sulphoxides used in the kinetic resolution experiments above are included in the Table. The sulphoxides, except for aryl benzyl sulphoxides,§ were produced in good yields. Alkyl phenyl sulphoxides were produced with optical purities of 40—70% while alkyl *p*-tolyl sulphoxides showed very low optical purities although all the sulphoxides were *R*-enriched.¶ If the oxidation was carried out with 10 mol. equiv. of hydrogen peroxide for a long time, interestingly, the optical purity of *R*-enriched (**2a**) increased gradually as the amount of sulphoxide decreased, reaching a constant value of 93% after 84—96 h, when the sulphoxide yield was 47%. This may be interpreted by stereoselective oxidation proceeding at the BSA chiral binding domain in two stages. Thus the *R*-enriched sulphoxide produced by the first stage oxidation was followed by preferential oxidation of the remaining *S* sulphoxide to increase the *R*/*S* ratio. Also in the oxidation of n-butyl phenyl sulphide (**1b**) and isobutyl phenyl sulphide (**1c**) preferential loss of the *S* sulphoxide increased the optical purities of initially produced 65% *R*-enriched sulphoxides, and maximum optical purities of 90 and 91% were obtained with, respectively, yields of 45 and 44% of sulphoxide. The oxidation of *p*-tolyl sulphides contrasted with the above phenyl sulphide oxidations. In this case kinetic resolution tended to lower the optical purity of the sulphoxide. For instance, n-butyl *p*-tolyl sulphide (**1g**) was oxidized to give 79% of the *R*-enriched sulphoxide in 17% optical purity. Further oxidation involving preferential loss of the *R* enantiomer resulted in a decrease to 13% optical purity of the *R* enantiomer when the sulphoxide yield was 57%.

Considered in combination with the results of kinetic resolution of racemic sulphoxides (Table), the preferential loss of the *S* enantiomer of alkyl phenyl sulphoxides and the less effective loss of the *R* enantiomer of alkyl *p*-tolyl sulphoxides, resulted both from the complex formed by BSA and a racemic sulphoxide and the enantiomeric sulphoxide produced by oxidizing the sulphide beforehand bound at the BSA binding domain. It is likely that the optical purity and configuration of the sulphoxide produced by the two-stage oxidation are the cumulative result of stereoselective processes in each stage of sulphide and sulphoxide oxidations. Since enantiomeric sulphoxides with a different configuration are often formed in the microbial oxidation of sulphides and racemic sulphoxides, an analogous mechanism might be postulated for the two-stage oxidation in microbial systems.

Thus, the findings described here show successfully a biomimetic approach to the high stereoselectivity which is characteristic of an enzyme reaction.

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‡ 1/3 mol. equiv. of BSA and pH >9 of buffer solution were needed to attain the maximum optical purities of the sulphoxides produced from the oxidation of the sulphides.

§ The formation yields of aryl benzyl sulphoxides were low (*ca.* 30%) because over-oxidation was unavoidable.

¶ Compared to the previous metaperiodate oxidation (see ref. 1) the use of hydrogen peroxide made the oxidation more stereocontrolled.

[1] For previous article on stereoselective reactions in chiral binding sites see T. Sugimoto, T. Kokubo, J. Miyazaki, S. Tanimoto, and M. Okano, *J.C.S., Chem. Comm.*, 1979, 402.

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