# Preparation of Optically Active Aromatic Sulphoxides of High Optical Purity by the Direct Oxidation of the Sulphides in the Presence of Bovine Serum Albumin

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*Summary* Aromatic sulphides were oxidized with sodium metaperiodate in the presence of bovine serum albumin to give the corresponding sulphoxides of high optical purity (81% max.) in good chemical yields.

ASYMMETRIC oxidation of sulphides with several reagents (optically active peracids,[1] iodine in the presence of a chiral catalyst,[2] or microbes[3]) provides sulphoxides, usually of low optical purity. We have now obtained optically active aromatic sulphoxides of considerably higher optical purity from the direct oxidation of the corresponding sulphides in the presence of bovine serum albumin (BSA); BSA also acted as a chiral binding site leading to high stereoselectivity in our earlier study of the asymmetric reduction of aromatic ketones.[4]

BSA, a carrier protein in biological systems, forms aggregates with various kinds of hydrophobic compounds.[5] Equilibrium dialysis experiments showed that aromatic sulphides are also good guest compounds for BSA. Effective discrimination of the enantiotopic electron pairs of prochiral sulphur atoms in sulphides should be achievable by fixing the sulphide in the chiral environment of BSA, thus making asymmetric induction in the subsequent oxidation possible. When the aromatic sulphides (**1**) (5·0 mM) were oxidized with sodium metaperiodate ($NaIO_4$) (25·0 mM) in a 0·05 M borate buffer solution (pH 9·2) containing BSA (Armour Fraction-V) in the concentration range 0·3—2·0 mM (the molecular weight of BSA was taken as 66,000), the optical purities of the resultant optically active sulphoxides (**2**) increased gradually with increasing amounts of BSA, reaching maximum values at 1·5—1·7 mM. The oxidations produced optically active sulphoxides of high optical purity (*ca.* 80%) in two cases [(**2c**) and (**2f**)] and modest optical purity for the other sulphoxides, except for the alkyl benzyl sulphoxides which were of very low optical purity (Table). In general, higher stereoselectivity is observed with increased branching of the alkyl group when the aryl group is phenyl; this is not

the case for *p*-tolyl and benzyl systems, however. It should be noted that the stereoselectivity and configuration change dramatically from the oxidation of alkyl phenyl sulphides to that of alkyl *p*-tolyl sulphides. This shows the great sensitivity of this method to changes in substrate structure at positions remote from the sulphur atom. Such a sensitivity is often encountered in microbiological oxidation, but it would not be expected from experience with

figuration was also *R*. Oxidation of BSA itself by these oxidizing reagents and resulting structural changes were unavoidable; if the BSA was reused in these oxidations sulphoxides of decreased optical purity resulted.

There are two remarkable features of this asymmetric oxidation. First, 1/3 mol. equiv. of BSA was needed to attain the maximum optical purity of the optically active sulphoxides produced from the oxidation of the sulphides

TABLE. Asymmetric oxidation of aromatic sulphides (**1**) with sodium metaperiodate in a 0·05 M borate buffer solution (pH 9·2) containing bovine serum albumin (BSA) at 25 °C.

| | Aromatic sulphide[a] $R^1$–S–$R^2$ (**1**) | | | Aromatic sulphoxide $R^1S(:O)R^2$ (**2**) | | | |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | Chemical yield[b]/% | $[\alpha]_D^{25}$/° (*c*, solvent) | Optical purity[c]/% | Chirality | Ref. |
| (**a**) | Ph | Me | 47 | +11·9 (0·8, $CHCl_3$) | 7 | *R* | [d] |
| (**b**) | Ph | Et | 58 | +51·0 (1·7, EtOH) | 29 | *R* | [e] |
| (**c**) | Ph | $Pr^i$ | 78 | +137·6 (1·6, $Me_2CO$) | 81 | *R* | [e] |
| (**d**) | Ph | $Bu^n$ | 87 | +64·4 (2·0, EtOH) | 36 | *R* | [e] |
| (**e**) | Ph | $Bu^i$ | 86 | −52·2 (2·0, EtOH) | 22 | *S* | [e] |
| (**f**) | Ph | $Bu^t$ | 86 | +135·3 (2·0, EtOH) | 75 | *R* | [d] |
| (**g**) | Ph | $C_6H_4Me$-*p* | 29 | −7·6 (0·8, EtOH) | 28 | *S* | [f] |
| (**h**) | Ph | $PhCH_2$ | 52 | +124·4 (1·4, $Me_2CO$) | 49 | *R* | [g] |
| (**i**) | $C_6H_4Me$-*p* | Me | 52 | +8·3 (1·0, EtOH) | 6 | *R* | [f] |
| (**j**) | $C_6H_4Me$-*p* | Et | 69 | −61·4 (1·5, EtOH) | 35 | *S* | [f] |
| (**k**) | $C_6H_4Me$-*p* | $Pr^i$ | 82 | −60·6 (1·9, EtOH) | 34 | *S* | [f] |
| (**l**) | $C_6H_4Me$-*p* | $Bu^n$ | 86 | −96·7 (2·1, $Me_2CO$) | 52 | *S* | [f] |
| (**m**) | $C_6H_4Me$-*p* | $Bu^t$ | 64 | +66·4 (1·6, EtOH) | 35 | *R* | [f] |
| (**n**) | $C_6H_4Me$-*p* | $PhCH_2$ | 50 | +99·7 (1·4, $Me_2CO$) | 40 | *R* | [h] |
| (**o**) | $PhCH_2$ | Me | 54 | +2·7 (1·0, EtOH) | 2 | *S* | [f] |
| (**p**) | $PhCH_2$ | Et | 27 | −10·5 (0·6, $CHCl_3$) | 10 | *S* | [f] |
| (**q**) | $PhCH_2$ | $Pr^n$ | 67 | +2·4 (1·5, EtOH) | 4 | *S* | [e] |
| (**r**) | $PhCH_2$ | $Bu^n$ | 60 | −1·6 (1·5, $CHCl_3$) | 1 | *S* | [i] |
| (**s**) | $PhCH_2$ | $Bu^t$ | 77 | +15·2 (1·9, EtOH) | 5 | *R* | [i] |
| (**t**) | $PhCH_2$ | *p*-$Bu^tC_6H_4$ | 43 | +22·3 (1·5, $Me_2CO$) | 10 | *R* | [g] |

[a] [Aromatic sulphide] = 5·0 mM, [$NaIO_4$] = 25·0 mM, and [BSA] = 1·5—1·7 mM. [b] The sulphoxides were isolated pure by preparative silica gel t.l.c. and showed satisfactory spectral data. [c] Optical purities were calculated from literature data (see last column) for the pure enantiomers. [d] U. Folli, D. Iarossi, F. Montanari, and G. Torre, *J. Chem. Soc.* (*C*), 1968, 1317. [e] M. Mikoajczyk and J. Drabowicz, *J. Amer. Chem. Soc.*, 1978, **100**, 2510. [f] K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, *J. Amer. Chem. Soc.*, 1965, **87**, 1958. [g] B. J. Auret, D. R. Boyd, H. B. Henbest, and S. Ross, *J. Chem. Soc.* (*C*), 1968, 2371. [h] C. J. M. Stirling, *J. Chem. Soc.*, 1963, 5741. [i] K. Mislow, M. M. Green, and M. Raban, *J. Amer. Chem. Soc.*, 1965, **87**, 2761.

optically active peracid oxidations. The Table shows that there is no regular pattern in the configuration of the sulphoxides which are obtained in enantiomeric excess on changing the alkyl and aryl substituents. The metaperiodate oxidations selectively gave sulphoxides with only a small amount of sulphones.[6] This excludes the possibility that most of the optical activity of the sulphoxides arises *via* the pathway involving relatively unselective oxidation of the sulphides followed by partial but highly stereoselective loss of one of the enantiomeric sulphoxides in each pair by oxidation to the sulphone. When other reagents such as *m*-chloroperbenzoic acid and hydrogen peroxide were used for the oxidation of sulphides to sulphoxides, lower optical purities were obtained or overoxidation was unavoidable. Oxidation of isopropyl phenyl sulphide (**1c**) with *m*-chloroperbenzoic acid selectively gave the (*S*)-sulphoxide with only a small amount of the sulphone, with an optical purity of 35%. Oxidation of (**1c**) with hydrogen peroxide although giving an increasing amount of the sulphone, led to a sulphoxide with an optical purity (78%) as high as that in the $NaIO_4$ oxidation; the con-

investigated. This can be interpreted as evidence for binding of about 3 sulphide molecules per BSA molecule. Considered in combination with the presence of 3 main binding domains in BSA, as shown recently by small-angle *X*-ray scattering,[7] binding of one sulphide molecule per domain is believed to be the most probable mode. Secondly, the optical purity was strongly dependent on the pH value of the buffer solution used. For example, the oxidation of (**1c**) was investigated in the pH region 3·1—12·3. At pH 9—12 the (*R*)-sulphoxide was obtained with an optical purity of 81%. However, at pH 8 and in the pH range 8—5, the (*S*)-sulphoxide was obtained in much lower (19%) optical purity. At pH values <5 the sulphoxide obtained was optically inactive. The dramatic changes near pH 5 and 8 in the asymmetric induction may be correlated with conformational changes in the gross protein structure, where the changes are well documented as N–F[8] and N–B[9] transitions, respectively.

The present method for the preparation of optically active aromatic sulphoxides is satisfactory in view of the chemical yields and optical purity obtained. However,

the synthetic utility of the method is still limited by the fact that BSA must be used in a near stoicheiometric amount and also that it cannot be reused repeatedly. It is commercially available and comparatively inexpensive, however.

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