Asymmetric Periodate Oxidation of Functionalized Sulfides Catalyzed by Bovine Serum Albumin

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The asymmetric oxidation of the functionalized sulfides with sodium metaperiodate in the presence of a catalytic amount of bovine serum albumin (BSA) affords the corresponding sulfoxides with enantiomeric excess (ee) up to 69.3%. The influence of the molecular structure of the substrate and of the pH value of the buffer solution on the asymmetric synthesis has also been examined.

Serum albumin, the most abundant protein in blood plasma, acts as a transport protein and can be easily purified on a large scale. It has an α helix content $\geq 75\%$[1] and presents hydrophobic residues between the helices capable of including water-insoluble guest substrates. This ability in binding noncovalently small molecules represents an attractive feature as a chiral tool for asymmetric synthesis.

Indeed asymmetric reductions of alkyl aryl ketones as well as stereoselective oxidation of aromatic sulfides and sulfoxides lead to optically active products with high ee.[2] More recently enantioselective cis-hydroxylation of alkenes[3] and hydrolysis of *p*-nitrophenyl esters[4] have been reported, showing in the latter case that BSA behaves as an enzyme, even though a poor one.

Here we report that bovine serum albumin can be used in catalytic amount to afford optically active functionalized sulfoxides, which are useful intermediates in the synthesis of a series of chiral products.[5]

$$\underset{\mathbf{1}}{\mathrm{ArSCH_2X}} \xrightarrow[\text{catalyst}]{\text{aq NaIO}_4} \underset{\mathbf{2}}{\mathrm{Ar\overset{*}{S}(=O)CH_2X}}$$

1a, **2a**, X = CO_2-*t*-Bu; Ar = *p*-MeC_6H_4

1b, **2b**, X = CO_2Ph; Ar = *p*-MeC_6H_4

1c, **2c**, X = CO_2Et; Ar = *p*-MeC_6H_4

1d, **2d**, X = COPh; Ar = *p*-MeC_6H_4

1e, **2e**, X = CO-*t*-Bu; Ar = *p*-MeC_6H_4

1f, **2f**, X = COMe; Ar = $PhCH_2$

1g, **2g**, X = $CONMe_2$; Ar = *p*-MeC_6H_4

The reactions were carried out by stirring at room temperature a heterogeneous mixture of substrate (1 mol) and $NaIO_4$ (2 mol) in the presence of BSA (0.05 mol) in a borate buffer solution (pH 9).

As starting sulfide we used esters **1a–c**, ketones **1d–f**, and the amide **1g**. The oxidation of *N,N*-dimethyl-*p*-toluenesulfenamide **1h** to the corresponding sulfinamide **2h** under the same reaction conditions has also been examined.

Table I. Oxidation of Sulfides 1a–h with $NaIO_4$ in a Buffer Solution Containing BSA at 25 °C

no.	pH	$[\alpha]_D$, deg	yield, %	ee, %	abs confign
1a	9	+103.2	60	69.3[a]	*R*
1a	7	+93	70	63	*R*
1a	11	+69.3	77	43.4	*R*
1b	7	+13	25	14[b]	*R*
1c	7	+6.2	68	10 ± 2[c]	
1d	9	+38.1	35	21[d]	*R*
1e	9	−56.6	55	35[e]	*S*
1f	7	−3.2	66	2.9[f]	*R*
1g	9	−23	45	11.8[g]	*S*
1g	7	−20.7	65	10.6	*S*
1h	9	−13.7	30	11.5[h]	*R*
1h	7	−5.15	60	4.3	*R*

[a] Maximum value for $[\alpha]_D$ +149° (*c* 2.25 in EtOH).[5] [b] Maximum value for $[\alpha]_D$ +87° (*c* 0.95 in $CHCl_3$).[7] [c] Determined by ^1H NMR spectroscopy with $Eu(hfc)_3$ as chiral shift reagent. [d] Maximum value for $[\alpha]_D$ +180.9° (*c* 1 in $CHCl_3$).[6] [e] Maximum value for $[\alpha]_D$ +162° (*c* 1 in $CHCl_3$).[6] [f] Maximum value for $[\alpha]_D$ −110° (*c* 1.65 in $CHCl_3$).[8] [g] Maximum value for $[\alpha]_D$ +194.7° (*c* 1 in $CHCl_3$).[9] [h] Maximum value for $[\alpha]_D$ +110° (*c* 1 in EtOH), ee 92%.[10]

Since β-keto sulfoxides can easily be reduced to the corresponding β-hydroxy derivatives by sodium borohydride,[6] it was worthwhile to investigate the stereoselectivity of this process with BSA (0.05 mol equiv) at pH 9.

Furthermore double asymmetric induction can be at work when one of the two enantiomers of β-keto sulfoxide **2d** is reduced with aqueous $NaBH_4$ and the protein as catalyst.

$$\underset{\mathbf{2d}}{p\text{-}MeC_6H_4S(=O)CH_2COPh} \xrightarrow{NaBH_4} \underset{\mathbf{3d,e}}{p\text{-}MeC_6H_4\overset{*}{S}(=O)CH_2C(OH)HPh} \rightarrow \underset{\mathbf{4d}}{p\text{-}MeC_6H_4SO_2CH_2\overset{*}{C}(OH)HPh}$$

Results

The results collected in Table I show that the oxidation of ester **1a** occurs with satisfactory chemical yield. The highest optical rotation $[\alpha]_D$ +103.20 of (*R*)-(+)-*tert*-butyl sulfinylacetate **2a** was obtained with 0.05 mol equiv of BSA

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in a borate buffer solution at pH 9 corresponding to 69.3% ee. The enantioselectivity is similar in a phosphate buffer solution at pH 7 (63% ee), and it decreases at pH 11 (43.4% ee). The use of H_2O_2 in place of $NaIO_4$ revealed less stereoselectivity; at pH 9 the (*S*)-(−)-ester **2a** was obtained in 19.7% chemical yield, $[\alpha]_D$ −4.8° (*c* 4 in EtOH, 3% ee). Thus the nature of the oxidizing agent determines the chirality of the reaction product.

In contrast with the results obtained by Sugimoto[2a] in the oxidation of aromatic sulfides the optical purity of **1b** decreased with an increasing amount of BSA at pH 9; indeed the use of 0.1 mol equiv of BSA led in a quantitative yield to the sulfinyl ester **2a** with $[\alpha]_D$ +74°.

When the aqueous protein solution was recycled twice in the usual reaction conditions (0.05 mol equiv of BSA at pH 9), it afforded the *tert*-butyl sulfinylacetate **2a** having $[\alpha]_D$ +77° in 60% chemical yield.

The oxidation of esters **1b** and **1c** at pH 7 gave the corresponding sulfoxides **2b** and **2c** having the *R*-(+) absolute configuration, with ee of 14% and 21%, respectively.

It is evident from the table that the *tert*-butyl group as a substituent enhanced the enantioselectivity also in the oxidation of β-keto sulfides, the optical purity of sulfoxide **2e** being higher than that of compounds **2d** and **2f**. Furthermore it should be pointed out the β-keto sulfoxides **2d** and **2e** have opposite chirality with respect to the benzyl derivative **2f**.

A low level of stereoselectivity was achieved in the conversion of the acetamido derivative **1g** to the (*S*)-(−)-sulfoxide **2g** at pH 7, (10.6% ee). A similar trend was observed in the formation of (*R*)-(−)-*N*,*N*-diethyl-*p*-toluenesulfinamide **2h**, the optical purities being 11.5% and 4.3% at pH 9 and 7, respectively. Due to the hydrolytic enzymelike behaviour of BSA[4] in the former case the chemical yield dropped to 30%.

The second part of this paper deals with the possibility of increasing the efficiency of asymmetric synthesis by the synergistic effect of the chiralities of the substrate and of the BSA used as catalyst.

For these reasons we prepared[6] enantiomerically pure (*R*)-(+)-β-keto sulfoxide **2d** and examined its reduction with aqueous $NaBH_4$ at pH 9, both in the presence and in the absence of the protein (0.05 mol equiv).

In order to determine the degree of asymmetric induction, the diastereomeric mixture of hydroxy sulfoxide **3d** and **3e** was oxidized to the corresponding sulfone **4d**.

In the former case β-hydroxy sulfone **4d** had $[\alpha]_D$ +8.58° (*c* 1.2 in $CHCl_3$, 43% ee); in the latter it had $[\alpha]_D$ +1.14° (*c* 3.6 in $CHCl_3$, 5.7% ee). The same procedure repeated starting from the racemic β-keto sulfoxide **2d** gave the β-hydroxy sulfone having $[\alpha]_D$ +2.75 (*c* 3.82 in $CHCl_3$, 14% ee).

Discussion

The oxidation of the difunctional sulfides described in this paper in aqueous medium with $NaIO_4$ and BSA always affords optically active products, although only in the case of (*R*)-(+)-*tert*-butyl sulfinylacetate **2a** the stereoselectivity is satisfactory. A large gap remains in the understanding of the process involved in these asymmetric syntheses. Nevertheless our results demonstrate that the use of catalytic amounts of the bovine serum albumin is not limited to the oxidation of formaldehyde di-*p*-tolyl dithioacetal and of alkyl aryl sulfide[2c] but can be extended to substrates having different functional groups. The absence of a noticeable pH dependence of stereoselectivity, in the range of pH 7–11, is another characteristic of this asymmetric oxidation, in contrast with the results previously found by Sugimoto and co-workers. Only the chemical yield of sulfinyl esters **2c** and **2d** and of the amides **2g** and **2h** are decreased by the use of buffer aqueous solutions having pH >7, as a consequence of the competitive hydrolysis.

These results as a whole seem to reduce the importance for the enantioselectivity previously attributed to the conformational changes in the protein occurring near pH 7–9, which have dramatic effects in the oxidation of alkyl aryl sulfides.[2a] Also the presence of a number of specific binding sites located on bovine serum albumin is of limited importance, at least for the high ligand to albumin ratios used in this work. In this regard it should be mentioned that the maximum optical yields in borohydride reduction of ketones[2b] and in the oxidation of alkyl aryl sulfides[2a] were obtained with a BSA/substrate ratio 1:3 as a result of the three main binding domains in the native BSA.

The high stereoselectivity observed in the presence of catalytic amounts of the protein may be attributed to the existence of less specific binding sites (>20) or to its denaturation.[2a]

The increased enantioselectivity exhibited by the *tert*-butyl group as substituent either in the oxidation of esters and of β-keto sulfides (69.3% and 35% ee in the case of compounds **2a** and **2e**, respectively) must be pointed out.

In this connection it should be reminded that the oxidation of *p*-tolyl *tert*-butyl sulfide with $NaIO_4$ and a much higher amount of BSA ($^1/_3$ mol equiv) lead to the corresponding sulfoxide with 35% ee.[2a] On the other hand the excellent catalytic new route to chiral sulfoxide, recently described by Kagan,[11] gave poor results in the oxidation of the *tert*-butyl *p*-tolylthioacetate **1a** (4% ee). The higher asymmetric bias observed by us for the butyl derivative **1a** may possibly be a manifestation of its closer proximity to the "active site" of the globular protein.

In the borohydride reduction the cooperativity between the chiralities of both the substrate and the catalyst is efficient, since the stereoselectivity is increased starting from the optically active sulfoxide **2d** and BSA.

Although albumin is able to bind many different ligands, its binding constant and binding specificity may be critically dependent on the presence of a particular chemical group, thus causing great changes in the ligand–protein interaction.

Experimental Section

General Methods. Melting points are uncorrected. The optical rotations were determined with a Perkin Elmer R 241 polarimeter. ^1H NMR spectra were recorded in $CDCl_3$ and the chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si on a Varian 90 instrument. Enantiomeric excesses were determined by ^1H NMR with the aid of $Eu(hfc)_3$ as shift reagent by using a Varian XL 200 instrument. BSA was the fraction V Fluka commerical product.

Preparation of the Functionalized Sulfides 1a–g. All these compounds were prepared according to the method of O. Newell and P. K. Calaway[12] by reaction of the thiolate and the properly functionalized alkyl halide. The benzylmercaptan and the *p*-thiocresol were commercial products as well as the *tert*-butyl chloroacetate, the ethyl chloroacetate, the α-chloroacetophenone, and the chloroacetone. The phenyl chloroacetate,[13] the pivaloyl chloride,[14] and the *N*,*N*-dimethylchloroacetamide[15] were prepared according to the literature and their physical properties were in

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agreement with those reported. The sulfides **1c,d,f** were known products[16,17,12] and their physical properties were in agreement with literature values.

***tert*-Butyl 1-(*p*-tolylthio)acetate (1a)** obtained in 80% yield had bp 115 °C (0.5 mm): n^{22}_D 1.5240; ^{1}H NMR δ 1.4 (s, 9 H), 2.3 (s, 3 H), 4.4 (s, 2 H), 7.1 (dd, 4 H). Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.5; H, 7.6. Found: C, 65.3; H, 7.7.

Phenyl 1-(*p*-tolylthio)acetate (1b) obtained in 56% yield after chromatography on silica gel petrol/diethyl ether 8:2 as eluant had mp 34–35 °C: ^{1}H NMR δ 2.3 (s, 3 H), 3.6 (s, 2 H), 7.1 (m, 9 H). Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.7; H, 5.5. Found: C, 69.4; H, 5.4.

1-(*p*-Tolylthio)-3,3-dimethyl-2-butanone (1e) obtained in 60% yield had bp 110 °C (0.05 mm): n^{25}_D 1.5408; ^{1}H NMR δ 1.1 (s, 9 H), 2.3 (s, 3 H), 3.8 (s, 2 H), 7.1 (dd, 4 H). Anal. Calcd for $C_{13}H_{18}OS$: C, 70.2; H, 8.2. Found: C, 70.3; H, 8.1.

1-(*p*-Tolylthio)-*N*,*N*-dimethylacetamide (1g) obtained in 53% yield after chromatography on silica gel with diethyl ether as eluant had mp 45 °C: ^{1}H NMR δ 2.3 (s, 3 H), 3.0 (d, 6 H), 3.7 (s, 2 H), 7.2 (dd, 4 H). Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.1; H, 7.2; N, 6.7. Found: C, 63.0; H, 7.2; N, 6.6.

Preparation of *N*,*N*-Diethyl-4-methylbenzenesulfenamide (1h). This compound, prepared according to the general method[18] by reaction of *p*-tolylsulfenyl chloride and diethylamine in dry ether, had bp 84 °C (0.5 mm): n^{24}_D 1.5387; ^{1}H NMR δ 1.3 (t, 6 H), 2.4 (s, 3 H), 3.1 (q, 4 H), 7.2 (dd, 4 H). Anal. Calcd for $C_{11}H_{17}NS$: C, 67.6; H, 8.7; N, 7.2. Found: C, 67.3; H, 8.4; N, 7.0.

Oxidations: Typical Procedure. The sulfide (1 mmol) and 3.3 g of BSA (5×10^{-2} mmol) were magnetically stirred in 12.5 mL of buffer solution for 2 h at 20 °C, then $NaIO_4$ (2 mmol) was added, and the mixture was kept stirring for 2 h. Extraction with 3 portions (70 mL each) of diethyl ether and evaporation of the organic layer after drying gave the crude product that was purified by chromatography on silica gel with mixtures of ether and petrol as eluant. The yields and optical rotation values are reported in Table I.

Characteristics of the Sulfoxides 2a–f and of the Sulfinamide 2h. *tert*-Butyl α-(*p*-tolylsulfinyl)acetate (**2a**) had n^{22}_D 1.5262: ^{1}H NMR δ 1.4 (s, 9 H), 2.4 (s, 3 H), 3.7 (dd, 2 H), 7.4 (dd, 4 H). Phenyl 1-(*p*-tolylsulfinyl)acetate (**2b**) had n^{22}_D 1.5100: ^{1}H NMR δ 2.4 (s, 3 H), 3.7 (dd, 2 H), 7.2 (m, 9 H). Ethyl 1-(*p*-tolylsulfinyl)acetate (**2c**) had n^{22}_D 1.5453: ^{1}H NMR δ 1.3 (t, 3 H), 2.4 (s, 3 H), 3.7 (dd, 2 H), 4.1 (q, 2 H), 7.4 (dd, 4 H). Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.4; H, 6.2. Found: C, 58.2; H, 6.1. α-(*p*-Tolylsulfinyl)acetophenone (**2d**) had mp 75–80 °C: ^{1}H NMR δ 2.4 (s, 3 H), 4.3 (dd, 2 H), 7.3 (m, 7 H), 7.8 (m, 2 H). 1-(*p*-Tolylsulfinyl)-3,3-dimethyl-2-butanone (**2e**) had mp 93–96 °C: ^{1}H NMR δ 1.1 (s, 9 H), 2.5 (s, 3 H), 4 (dd, 2 H), 7.4 (dd, 4 H). 1-(Benzylsulfinyl)propan-2-one (**2f**) had mp 100–103 °C: ^{1}H NMR δ 2.3 (s, 3 H), 3.5 (dd, 2 H), 4.1 (dd, 2 H), 7.3 (s, 5 H). 1-(*p*-Tolylsulfinyl)-*N*,*N*-dimethylacetamide (**2g**) had mp 65–68 °C: ^{1}H NMR δ 2.4 (s, 3 H), 2.9 (two s, 6 H), 3.8 (dd, 2 H), 7.4 (dd, 4 H). *N*,*N*-Diethyl-4 methylbenzenesulfinamide (**2h**) had n^{20}_D 1.5320: ^{1}H NMR δ 1.1 (t, 6 H), 2.5 (s, 3 H), 3.2 (q, 4 H), 7.3 (dd, 4 H).

Preparation of β-Keto Sulfoxides. The (+)-(*R*)-α-(*p*-tolylsulfinyl)acetophenone (**2d**) prepared according to literature,[6] had mp 80–81 °C, $[\alpha]_D$ +179 (*c* 1, $CHCl_3$). The racemic α-(*p*-tolylsulfinyl)acetophenone (**2d**), mp 80–82 °C, was prepared by reaction of the sulfide (**1d**) with $NaIO_4$ in the usual conditions.

Reduction of β-Keto Sulfoxides. The same general procedures described above for the oxidation was followed with $NaBH_4$ (2 mmol) as reducing agent in pH 9 buffer solution. When the optically active β-keto sulfoxide, $[\alpha]_D$ +179, was used the β-hydroxy sulfoxide was obtained in 91% yield as crude product whereas the same compound was obtained in 80% yield starting from the racemic parent compound. Both these products were oxidized by the stoichiometric quantity of *m*-chloroperbenzoic acid at 20 °C for 18 h to the β-hydroxy sulfone in 65% and 74% yield, respectively, after purification by column chromatography (silica–light petroleum ether 1:1). The former had $[\alpha]_D$ +8.58 (*c* 1.2 in $CHCl_3$), mp 65–70 °C, while the latter had $[\alpha]_D$ +2.75 (*c* 3.92 in $CHCl_3$): mp 55–60 °C; ^{1}H NMR δ 2.4 (s, 3 H), 3.2 (m, 2 H), 3.6 (broad s, 1 H), 5.1 (dd, 1 H), 7.1 (m, 7 H), 7.6 (d, 2 H). When the borohydride reduction at pH 9 was repeated with β-keto sulfoxide **2d**, $[\alpha]_D$ +179, the oxidation of the intermediate diastereomeric mixture afforded the corresponding sulfone, $[\alpha]_D$ +1.14 (*c* 1 in $CHCl_3$), mp 45–50 °C.

Registry No. **1a**, 36304-27-5; **1b**, 94404-17-8; **1c**, 14738-27-3; **1d**, 33046-45-6; **1e**, 94404-18-9; **1f**, 10230-69-0; **1g**, 94404-19-0; **1h**, 24398-14-9; (*R*)-(+)-**2a**, 58059-08-8; (*S*)-(−)-**2a**, 94404-20-3; (*R*)-(+)-**2b**, 75340-59-9; (*R*)-(+)-**2c**, 72298-24-9; (*R*)-(+)-**2d**, 52154-24-2; (±)-**2d**, 86783-32-6; (*S*)-(−)-**2e**, 68326-60-3; (*R*)-(−)-**2f**, 69164-59-6; (*S*)-(−)-**2g**, 94404-21-4; (*R*)-(−)-**2h**, 94481-26-2; **3d**, 39201-98-4; **3e**, 39201-99-5; (+)-**4d**, 71899-81-5.

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C-(Methoxycarbonyl)ketene *N*-Imidoylimines. Synthesis and Rearrangement into Methyl 4,6-Diazahepta-2,4,6-trienoates. Cycloaddition Reactions with Isocyanides: Preparation of Imidazolines

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The ketene *N*-imidoylimines **12** are shown to be transitory intermediates formed by the reaction of isocyanides with sulfides **1** or by the reaction of imino chloro sulfides with sodium salts of α-cyano esters **3**. When the nitrogen atom of the imidoyl group bears a primary or secondary substituent, the ketene imines **12** are converted into diazatrienes **13** by a very fast 1,5-migration of the hydrogen atom of the imidoyl group. Diazatrienes **13** that bear a cyano group on C-1 of the R^1 group undergo an intramolecular [4 + 2] cycloaddition to form dihydropyrrolotriazines **14**. The diazatrienes **13** can be trapped by a regiospecific [1 + 4] cycloaddition with isocyanides to give imidazolines.

Introduction

In previous work, *tert*-butyl isocyanide and *tert*-octyl isocyanide were reported to insert into the carbon–sulfur bond of the electrophilic sulfides **1**.[1] The first step of the reaction occurs via the heterolytic and reversible cleavage of the C–S bond, giving an ion pair **2**. The rearrangement of **2** gives the thioimidates **10**, which are rapidly isomerized into stable *N*-vinylcarbamates **11**. Thioimidates and the isomeric carbamates can be also prepared by the reaction of (*tert*-butylimino)chloro(methylthio)methane (**9**) with the α-cyano ester salts **3** (Scheme I).[1] Only the carbon

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