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ENANTIOSELECTIVE OXIDATION OF SULPHIDES TO SULPHOXIDES IN THE PRESENCE OF BOVINE SERUM ALBUMIN.

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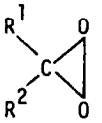
ABSTRACT. In situ generated dioxiranes oxidize a series of prochiral sulphides to the corresponding sulphoxides with enantiomeric excess (e.e.) up to 89%, when bovine serum albumin (BSA) is used as chiral auxiliary. The degree of enantioselectivity, as well as yield and reaction times, depend upon the nature of the dioxirane. These are compared with enantioselectivities attainable for the same transformations by using peroxomonosulfate alone, i.e. in the absence of ketone. In the oxidation of prochiral keto sulphides (wherein the carbonyl functionality serves as precursor of dioxirane) with peroxomonosulfate, optically active keto sulphoxides are isolated in satisfactory chemical and optical yield (up to e.e. 84%).

INTRODUCTION.

Dioxiranes (**1**), the smallest ring peroxides containing carbon, constitute a class of powerful and versatile oxidants that rank among the most useful recent additions to the chemistry tools available to synthetic chemists.[1] These reactive species can be employed either as generated in situ by the reaction of potassium peroxomonosulfate (caroate, an inexpensive inorganic salt) with ketones,[1a,2,3] or after isolation[4,5] as a solution in the parent ketone.



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1a: $R^1=R^2=CH_3$; **1b**: $R^1=CF_3$, $R^2=CH_3$
1c: $R^1=Ph$, $R^2=CF_3$ **1d**: $R^1,R^2=-CH_2(CH_2)_3CH_2-$

The unique characteristic of these strained peroxides as O-atom transfer reagents have been exploited to carry out a number of remarkable transformations, such as the selective oxyfunctionalization of saturated hydrocarbons[6,7] under astonishingly mild conditions,[7] and the direct conversion of silanes R_3Si-H into silanols R_3Si-OH.[8] Also conspicuous is the application of dioxiranes in the isolated form to the synthesis of labile epoxides that would be difficult to obtain otherwise, e.g. those derived from enol ethers,[9] enol lactones,[10] allenes,[11] and pyranose and furanose glycals.[12] Isolated dioxiranes are also excellent electrophilic oxygen transfer agents toward organonitrogen and organosulfur compounds.[1] For instance, a series of para substituted sulphides X-C_6H_4-SMe were converted cleanly into the corresponding sulphoxides using dimethyl- dioxirane (**1a**) by Murray and coworkers;[13] a Hammett value of -0.8 was determined for this reaction.

Prior to the applications of dioxiranes in the isolated form, it had been shown[2a] that in situ dioxiranes can be usefully employed to carry out a number of synthetically useful transformations,[1a] such as epoxidations of simple and functionalized alkenes,[2b] of allylic alcohols,[2c] and of polycyclic aromatic hydrocarbons.[3]

The various steps and the few limitations that attain in oxidations with in situ dioxiranes have been discussed in detail.[1a] In particular, during oxidation of compounds that are good nucleophiles such as the organic sulphides, with the in situ method it should be expected[1a] that oxidation by peroxomonosulfate (which is present in large excess) can compete with dioxirane oxidation. In fact, it is known that peroxomonosulfate is itself a convenient reagent for the oxidation of sulphides to sulphoxides,[14,15] and of these to sulphones.[16]

Enantioselective epoxidations using dimethyldioxirane generated in situ from chiral ketones have been reported.[2d] Also, thianthrene-5-oxide has been oxidized using dimethyldioxirane (**1a**),[17] and, more recently, excellent diastereoselective sulphide oxidations have been achieved using caroate in acetone as solvent.[14] In view of the versatility of these new reagents, it is perhaps surprising that their potential in asymmetric oxidation has not been probed, with one noticeable exception.[3d]

We therefore decided to explore the possibility of achieving appreciable enantioselectivity in the oxygen transfer to prochiral sulphides by in situ generated achiral dioxiranes in the presence of bovine serum albumin as chiral auxiliary and determining the effect of varying the nature of the substrate and of the ketone precursor. Preliminary results have been the subject of a communication.[18]

The sulphides employed were phenyl methyl (2), p-tolyl methyl (3), phenyl ethyl (4), p-tolyl ethyl (5), phenyl iso-propyl (6), p-tolyl iso-propyl (7), phenyl tert-butyl (8),

$$\underset{\text{2-13}}{\text{R-S-R'}} \xrightarrow[\text{BSA}]{\text{O}} \underset{\text{14-25}}{\text{R-S*(=O)-R'}}$$

p-tolyl tert-butyl (9), phenyl cyclohexyl (10), phenyl benzyl (11), benzyl methyl (12), and p-tolyl benzyl (13) sulphides.

We have also used caroate alone in the sulphoxidation of a series of functionalized sulphides, having a carbonyl group that can serve as the precursor of the dioxirane. Since it might be expected that intramolecular processes proceed at higher rate with respect to intermolecular ones, it was hoped that this would allow us to discriminate

$$\underset{\text{26-32}}{\text{R-S-(CH}_2\text{)}_n\text{-COR'}} \xrightarrow[\text{BSA}]{\text{O}} \underset{\text{33-39}}{\text{R-S*(=O)-(CH}_2\text{)}_n\text{-COR'}}$$

26,33	R = C_6H_5;	R' = CH_3;	n = 1
27,34	R = p-$CH_3C_6H_4$;	R' = CH_3;	n = 1
28,35	R = C_6H_5;	R' = $C_3H_7^i$;	n = 1
29,36	R = p-$CH_3C_6H_4$;	R' = $C_3H_7^i$;	n = 1
30,37	R = p-$CH_3C_6H_4$;	R' = $C_4H_9^t$;	n = 1
31,38	R = p-$CH_3C_6H_4$;	R' = C_6H_5;	n = 1
32,39	R = p-$CH_3C_6H_4$;	R' = CH_3;	n = 3.

between oxidation by caroate and oxidation by the in situ generated dioxiranes. The reactions were carried out by stirring a heterogeneous mixture of sulphide, BSA and oxidant in aqueous buffer (pH 7.2-7.8) at 4°C, either in the presence or absence of ketone. The crude products were purified by column chromatography (SiO_2, diethylether methanol 95:5 v/v as eluants). The e.e. were determined by ^1H NMR spectroscopy using $Eu(tfc)_3$ as chiral shift reagent and/or HPLC analysis on a Diacel Chiralcel OD column. Reaction conditions, chemical yields, absolute configurations and e.e. of sulphoxides are reported in Tables 1-4.

The majority of experiments were carried out using dimethyl dioxirane (1a) (Table 1). The data show that the highest e.e. were obtained starting from phenyl iso-propyl (6) and phenyl tert-butyl sulphide (8), 79% e 73% e.e., respectively. The presence of a methyl group in the para position of the phenyl ring has a variable effect on the degree of the

Table 1. Sulphoxidation with dimethyl dioxirane generated in situ.

Sulphide	Time(min)	Sulphoxide yield %	Sulphone yield %	e.e.%	Abs config.
2) Ph-S-Me	180	98	-	7	(S)-(-)
3) pTol-S-Me	60	77	-	32	(S)-(-)
4) Ph-S-Et	60	51	-	1	(R)-(+)
5) pTol-S-Et	105	68	-	64	(S)-(-)
6) Ph-S-Pr^i	120	56	5	79	(R)-(+)
7) pTol-S-Pr^i	120	50	11	29	(S)-(-)
8) Ph-S-Bu^t	120	70	-	73	(R)-(+)
9) pTol-S-Bu^t	85	40	14	9	(R)-(+)
10) Ph-S-C_6H_{11} [c]	25	45	5	52	(R)-(+)
11) Ph-S-Bz	180	30	14	68	(R)-(+)
12) Bz-S-Me	180	85	-	24	(S)-(-)

a) sulphide:$KHSO_5$:acetone:BSA ratio = 1/2/13/0.05.

enantioselectivity, since it increases the e.e. in the case of sulphides (3) and (5), but lowers it for sulphides (7) and (9). It should be also pointed out that the introduction of a para-methyl group has unforeeseable effects also on the stereochemical course of the reactions, giving either the same or the opposite configuration in the prevailing sulphoxide enantiomer, with respect to the corresponding unsubstituted phenyl alkyl sulphides. Sugimoto and co-workers had similar results in the oxidation of phenyl alkyl and p-tolyl alkyl sulphides with tert-BuOOH or H_2O_2 in the presence of BSA.[19]

In order to verify whether the stereochemistry of the sulphoxidation is due to a different recognition of the sulphides by the bovine serum, the equilibrium binding constants of phenyl iso-propyl (6) and phenyl ethyl (4) sulphides were measured, along with those of the corresponding para-tolyl analogous.

The results, collected in Table 5, show that the affinities of the various sulphides for the protein are very similar (association constants ranging from 1.33 to 1.90 $10^4 M^{-1}$), in spite of the structural differences especially remarkable in the case of ketosulphide (29). The affinity of sulphoxides was approximately 50% of the corresponding sulphides. The data also show that in all cases one mole of BSA binds only one mole of ligand.

Table 5. Binding of sulphides and sulphoxides to BSA.

ligand	association constants (M^{-1})	mol ligand / mol BSA
p-Me-Ph-S-Pr^i	$1.33\ 10^4$	0.80
Ph-S-Pr^i	$1.60\ 10^4$	0.81
Ph-SO-Pr^i	$0.76\ 10^4$	0.83
p-Me-Ph-S-Et	$1.54\ 10^4$	0.85
Ph-S-Et	$1.35\ 10^4$	0.90
p-CH_3-Ph-S-CH_2-CO-Pr^i	$1.90\ 10^4$	0.78
p-CH_3-Ph-SO-CH_2-CO-Pr^i	$0.97\ 10^4$	0.83

The results of competition studies, reported in Table 6, indicate that an excess of a second ligand (competitor), either sulphide or sulpho xide, almost completely inhibited the binding of the first ligand to BSA. This leads to the conclusion that the various sulphides and sulphoxides interact with the same binding site on BSA.

Table 6. Competition among various ligands for BSA binding site.[a]

ligand	competitor	free ligand (M) control	with BSA	with BSA and 110 M competitor
Ph-S-Et	p-CH_3-Ph-S-Et	16.0	9.5	14.0
	Ph-S-Pr^i	16.0	9.5	14.2
Ph-S-Pr^i	p-CH_3-Ph-S-Pr^i	16.0	9.1	13.8
	Ph-SO-Pr^i	16.0	9.1	12.9

[a] For experimental detail see Experimental Section.

Therefore the different enantioselectivities in the oxidation of phenyl alkyl and para tolyl alkyl sulphides cannot be ascribed to varying association constants with BSA, but rather to a different conformational arrangement of the protein environment. In most cases the competitive oxidation of sulphoxide to sulphone is not substantial, with the exception of the phenyl benzyl derivative (11). Most likely the presence of the BSA in the reaction medium protects the sulphoxide from the further oxidation to sulphone. This is suggested by the results obtained in the oxidation of phenyl iso-propyl sulphide (6) with caroate and acetone; in fact in the presence of BSA no detectable amounts of the sulphone were formed, whereas in its absence the sulphone yield was 40%. The finding that bovine serum albumin prevents further oxidation of sulphoxides to sulphones must be due to the fact that this protein can be a target for the oxidation by potassium caroate or in situ generated dioxiranes. Indeed we have observed that with these oxidants some Cys residues where transformed into cysteic acid. As expected, when BSA was incubated with both oxidants but in the presence of a sulphide, the number of cysteic acid units was lower.

The asymmetric induction in the sulphoxidation reaction is accompanied by a negligible kinetic resolution (2% enrichment in favor of (+) (18) in the oxidation of racemic phenyl iso-propyl sulphoxide (18) to the corresponding sulphone under the usual reaction conditions.

The degree of stereoselectivity and reaction rates depend upon the structure of the dioxirane (Table 2). In situ generated methyl trifluoromethyl dioxirane (1b) yielded the highest enantioselectivity (89% e.e.) observed in the oxidation of phenyl iso-propyl sulphide (6). Phenyl iso-propyl sulphoxide (18) of lower optical purity (16% e.e.) was obtained with the dioxirane (1d) deriving from cyclohexanone. An intermediate behaviour was observed with trifluoroacetophenone as dioxirane precursor (64% e.e.).

The reaction times were in the range 0.4-4h depending upon the structure of the substrate and of the parent ketone. As expected with methyl trifluoromethyl dioxirane (1b), which is by far more reactive than (1a)[5,7] higher oxidation rates were recorded.

All of the dioxiranes displayed the same stereochemical course with the exception of the trifluoroaceto- phenone dioxirane (1c); the latter, in fact, surprisingly afforded the (+)-(R) p-tolyl sulphoxide (15) instead of (-)-(S) (15), as found with the dimethyldioxirane species (1a).

Starting with sulphides in aqueous buffer solution in the presence of a catalytic amount of BSA we have also tested the enantioselectivity attainable using potassium peroxymonosulfate alone (i.e. in the absence of ketone).

Table 2. Sulphoxidation with different dioxiranes generated in situ.

Sulphide	Starting ketone	Time (min)	Sulphoxide yield %	Sulphone yield %	e.e.%	Abs config.
3) pTol-S-Me[a]	$C_6H_5COCF_3$	135	80	-	9	(R)-(+)
3) pTol-S-Me[b]	$C_6H_{10}O$	240	60	-	6	(S)-(-)
3) pTol-S-Me[c]	CH_3COCF_3	10	78	5	4	(S)-(-)
5) pTol-S-Et[a]	$C_6H_5COCF_3$	180	78	-	43	(S)-(-)
5) pTol-S-Et[c]	CH_3COCF_3	60	66	12	61	(S)-(-)
6) Ph-S-Pr^i [a]	$C_6H_5COCF_3$	120	96	-	64	(R)-(+)
6) Ph-S-Pr^i [b]	$C_6H_{10}O$	120	46	-	16	(R)-(+)
6) Ph-S-Pr^i [c]	CH_3COCF_3	5	67	-	89	(R)-(+)
8) Ph-S-Bu^t [a]	$C_6H_5COCF_3$	90	37	10	71	(R)-(+)
8) Ph-S-Bu^t [c]	CH_3COCF_3	5	55	-	67	(R)-(+)
11) Ph-S-Bz[a]	$C_6H_5COCF_3$	150	22	3	73	(R)-(+)
11) Ph-S-Bz[c]	CH_3COCF_3	5	20	21	72	(R)-(+)
13) pTol-S-Bz[c]	CH_3COCF_3	5	95	-	38	(R)-(+)

a) Sulphide:$KHSO_5$:BSA:trifluoroacetophenone ratio = 1/2/0.05/1.3-0.44.

b) Sulphide:$KHSO_5$:BSA:cyclohexanone ratio = 1/2/0.05/13.

c) Sulphide:$KHSO_5$:BSA:trifluoroacetone ratio = 1/0.5-2/0.05-0.0125.

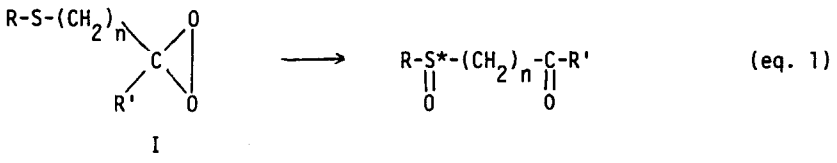
This was done in order to verify whether employing caroate alone or in situ generated dioxiranes would lead to different enantioselectivities and rates. The sulphoxide/sulphone ratios could also depend upon the nature of the oxidant. It should be noted that the results reported in Table 3 do not differ markedly from those obtained in sulphoxidations by dioxiranes. As a matter of fact, the main stereochemical course of the reaction was the same with both caroate and dioxiranes, with noticeable exception of the oxidation of p-tolyl methyl sulphide (3) by trifluoroacetophenone dioxirane (1c). Enantioselectivities are also of the same order of magnitude. However it should be noted that, under the same conditions, caroate alone has a tendency to carry the oxidation past the sulphoxide stage, producing higher amounts of sulphone.

Table 3. Sulphoxidation with $KHSO_5$.[a]

Sulphide	Time(min)	Sulphoxide yield %	Sulphone yield %	e.e.%	Abs config.
3) p-Tol-S-Me	60	72	13	13	(S)-(-)
4) Ph-S-Et	60	75	-	5	(R)-(+)
5) p-Tol-S-Et	105	41	18	64	(S)-(-)
6) Ph-S-Pr^i	120	74	14	79	(R)-(+)
7) p-Tol-S-Pr^i	5	62	13	17	(S)-(-)
8) Ph-S-Bu^t	120	67	19	88	(R)-(+)
9) p-Tol-S-Bu^t	10	74	-	20	(R)-(+)
10) Ph-S-Es[c]	45	42	14	54	(R)-(+)
11) Ph-S-Bz	130	24	29	72	(R)-(+)

[a] Sulphide/$KHSO_5$/BSA ratio = 1/2/0.05.

Ketosulphides present the attractive feature of having a carbonyl encompassed in the molecular framework. Reaction with caroate should lead to dioxiranic species of type I, so that the substrates might evolve to sulphoxides (33-39) via intramolecular oxygen transfer.



I

(eq. 1)

With the exception of dioxirane intramolecular epoxidation of enones,[2b] this would represent a novel approach to dioxirane oxidations. The results, collected in Table 4 , demonstrate that high reaction rates and selectivities are observed in most cases, since no sulphone is formed with the sole exception of p-tolyl-thioacetophenone substrate (27). It is worth noting that in spite of the varying degree of enantioselectivity observed (6-84%, e.e.), the prevailing stereochemical course of the oxidation is the same, since

Table 4. Sulphoxidation with $KHSO_5$.[a]

Ketosulphides	Time (min)	Sulphoxide yield %	Sulphone yield %	e.e.%	Abs config.
26) Ph-S-CH_2-CO-CH_3	40	100	-	6	(S)-(-)
27) p-Tol-S-CH_2-CO-CH_3	30	100	-	72[c]	(S)-(-)
28) Ph-S-CH_2-CO-Pr^i	10	84	-	35[b]	(S)-(-)
29) p-Tol-S-CH_2-CO-Pr^i	10	94	-	82[c]	(S)-(-)
30) p-Tol-S-CH_2-CO-Bu^t	30	83	-	79[c]	(S)-(-)
31) p-Tol-S-CH_2-CO-Ph	20	59	10	9	(S)-(-)
32) p-Tol-S-$(CH_2)_3$-$COCH_3$	140	63	-	84[c]	(S)-(-)

a) Ketosulphide/$KHSO_5$:BSA ratio = 1/2/0.05.

b) Measured by ^1H NMR.

c) Measured by HPLC.

the ketosulphoxides produced had all the (S) absolute configuration. As in the case of unfunctionalized sulphides, also with these substrates the presence of a methyl group in the para position of the phenyl ring has relevant consequences on the enantio selectivity. The binding constant and the number of molecules of -keto sulphide (29) bonded in saturating conditions to BSA are very similar to those found for the already mentioned alkyl aryl sulphides (Table 5). Again the corresponding sulfoxide (36) has a lower affinity for the protein.

Some ^{18}O-tracer studies carried out with carbonyl labelled sulphide (27) give an indirect evidence of intervention of a dioxiranic species of type I. As a matter of fact the exchange of ^{18}O carbonyl oxygen of this substrate with $H_2{}^{16}O$ in the caroate solution occurs at higher rate with respect to the exchange performed in the same conditions, but in the absence of oxidizing agent. The enhanced caroate decomposition by ketones and the loss of carbonyl label support the formation of dioxiranes as the reactive intermediates.[1a]

The results of the ^{18}O-tracer studies as a whole could be rationalized on the basis of the different concentration of the two oxidizing species (dioxirane and caroate) in the

reaction medium, since the concentration of the dioxiranic species at the equilibrium is very low. Moreover one should keep in mind that caroate is highly reactive towards organic sulphides. In fact according to Quallic[16] the oxidation of cyclic sulphides to sulphoxides with potassium peroxymonosulfate occurs faster than formation of the dioxirane intermediate.

In conclusion the asymmetric sulphoxidation of aryl alkyl sulphides both with dioxiranes generated in situ and with potassium peroxomonosulfate, in the presence of a catalytic amount of bovine serum albumin, is highly stereoselective. It compares favourably in terms of enantioselectivity and rate with those observed using H_2O_2 or tert-BuOOH as oxidants and a much larger amount of globular protein.[19] A higher selectivity in the formation of the corresponding sulphoxides is observed when caroate/ketone is used as oxidant, as shown by the negligible quantity of sulphone formed. With soluble ketosulphides as starting material the reaction with caroate is even faster and occurs in high chemical yields.

The involvement of dioxiranes is supported indirectly by the different enantioselectivities and reaction rates observed in the formation of aryl alkyl sulphoxides, when different ketones were used as dioxirane precursors. In line with this is also the opposite stereochemical course observed in the oxidation of p-tolyl methyl sulphide (3) with caroate and with the system caroate/trifluoroacetophenone (1c), respectively.

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EXPERIMENTAL SECTION

Proton NMR spectra were recorded in $CDCl_3$ on a Varian 390 instrument. Enantiomeric excesses were determined by ^1H NMR with the aid of $Eu(hfc)_3$ as chiral shift reagent using a Varian XL 300 instrument or by HPLC analysis on a Diacel Chiralcel OD column. For the dialysis experiments dialysis tubing for proteins MW 12000 (Sigma D-9277) were employed. Mass spectra were obtained on a VG Analytical 7070 EQ-HF instrument, equipped with its own standard EI source at 70 ev.

The optical rotations were measured on a Perkin-Elmer 377 polarimeter.

Materials. Aryl alkyl sulphides (2-9), (12) were prepared according to Sugimoto[19]. Phenyl

cyclohexyl sulphide (10) was obtained as already described[21]. Sulphides (11) and (13) were prepared according to Shriner[22] and Gilman[23], respectively. Ketosulphides (26-28), (30-32) were obtained, following Newell procedure[24]. The physical properties of ketosulphides (26-28), (30) and (31) were in agreement with those reported in the literature[24-28].

1-(p-Tolylthio)-3 methyl-2-butanone (29) was obtained in 67% yield after chromatography on silica gel with light-petroleum/diethyl ether as eluants: ^{1}H NMR 1.1 (d, 6H), 2.3 (s, 3H), 2.9 (m, 1H), 3.7 (s, 2H), 7.2 (dd, 4H). Anal. Calcd for $C_{12}H_{16}OS$: C, 69.5; H, 7.7. Found: C, 69.6; H, 7.6.

5-(p-Tolylthio)-2-pentanone (32) obtained in 70 yield had n_D^{20} 1.5350: ^{1}H NMR 1.85 (m, 2H), 2.1 (s, 3H), 2.3 (s, 3H), 2.5 (t, 2H), 2.85 (t, 2H), 7.2 (dd, 4H). Anal. Calcd for $C_{12}H_{16}OS$: C 69.5; H, 7.7. Found: C, 69.4; H, 7.6.

^{18}O(p-tolylthio) acetone was prepared by heating at 40°C for 7 days the corresponding isotopically normal ketosulphide (1.56 mmol) with $H_2{}^{18}O$ (97 atom % ^{18}O) (0.312 mL) in anhydrous dioxane (0.300 mL) in the presence of a catalytic amount of H_2SO_4. The reaction mixture was extracted with two portions (25 mL each) of chloroform, the organic layer was dried over Na_2SO_4 and evaporated to give the title compound in 79% yield, ^{18}O content 80% by MS.

BSA fraction V was a commercial product (Fluka). Commercial potassium peroxomonosulfate (Oxone, Du Pont Co.) was used with no further purification.

Catalytic oxidations. Typical Procedure. BSA (0.0375 mmol) was dissolved in water (7 mL), containing sodium bicarbonate (3.26 mmol) and traces of $(EDTA)Na_2$ under magnetic stirring. The sulphide was added and the reaction mixture was stirred for 2h at room temperature and then cooled at 4°C. After the dropwise addition of the ketone to the stirred heterogeneous mixture buffered at pH 7.2-7.8 a cold solution of oxone (1.5 mmol) in water (8 mL) was added dropwise, keeping the buffer aqueous solution at the same pH. Extraction with five portions (75 mL each) of diethyl ether, drying of the organic layer and evaporation gave the crude product. This was purified by flash chromatography (SiO_2) with mixtures of diethyl ether and methanol as eluents.

Characteristic of the Sulphoxides. Alkyl aryl sulphoxides 14-25 were all known in the optically active form, and the physical properties of our specimens were in agreement with those reported[19,29-31] Ketosulphoxides (33-38) were known in the optically active form and had physical properties in agreement with those reported[32].

5(p-Tolyl sulphinyl)-2 pentanone (39)was obtained as an oil, ^{1}H NMR 2.1 (s, 3H), 2.4 (s, 3H), 2.7 (m, 6H), 7.4 (dd, 4H). Anal. Calcd for $C_{12}H_{16}O_2S$: C, 64.2; H, 7.2. Found: C,

64.3; H, 7.1.

Binding studies. The binding of sulphides and sulphoxides to BSA was determined by dialysis. BSA (80 mg), dissolved in 2 ml of 0.1 M $NaHCO_3$, pH 8, was put inside the tubing (0.6 cm diameter, cellulose membrane, Sigma) and equilibrated (about 2h) under gentle stirring, at 25°C, with ligand solutions (in 10 ml of 0.1 M $NaHCO_3$, pH 8) of various concentrations. The concentration of free ligand was determined by spectrophotometric measurement of the solution outside the tubing at 245-256 nm, depending on the ligand. The amount of bound ligand was calculated by substracting the free ligand from the total amount of added ligand. The association constants, and the moles of ligand bound per mole of BSA were calculated using the ligand binding programme of Enzfitter[33].

Competition studies, designed to find out if the various ligands interacted with the same binding site on BSA, were also carried out by dialysis. BSA (500 mg), dissolved in 10 ml of 0.1 M $NaHCO_3$, pH 8, containing 16 M ligand, was put inside the tubing (2.1 cm diameter, cellulose membrane, Sigma) and equilibrated (3 h) under gentle stirring, at 25°C, with 40 ml of 0.1 M $NaHCO_3$, pH 8, 16 M ligand. Then, 20 ml of the solution outside the tubing (to which 20 g of n-dodecane were added as the internal standard) were extracted by shaking with 1.5 ml of diethyl ether, and centrifuged. Part of the organic layer was recovered and analyzed by GLC on a 25 m HP-1 capillary silica gel column coated with methyl silicone gum, with H_2 as the carrier gas, at 140°C, to determine the concentration of the free ligand. A similar binding experiment was carried out in the presence of an excess (110 M) of a second ligand (competitor). The control experiment was performed in the absence of both BSA and the competitor.

^{18}O-Tracer studies. ^{18}O(p-tolylthio)acetone, having 80% ^{18}O excess as indicated by the analysis of the molecular ion region of its EI spectrum (0.5 mmol) was stirred at 4°C for 15 min. with phosphate aqueous buffer pH 7.4 (10 ml). The reaction mixture was extracted with diethyl ether, dried and evaporated under vacuum. The recovered ketosulphide (27) had 54% ^{18}O content. Under the same conditions, but in the presence of caroate (0.25 mmol) sulphide (27) was converted into the corresponding sulphoxide (34), having a peak of m/z 196 (14%). Therefore in compound (34) both the sulphinyl and carbonyl oxygen are unlabelled. Another peak of m/z 198 (2.3%) is indicative of a small ^{18}O content left in the molecule. This ^{18}O label is only present in the carbonyl function, since the fragment ion due to $pCH_3C_6H_4SO^+$ appeares at m/z 139 (100%). This peak is accompanied by its isotopic ion m/z 141 (5%), in fair agreement with the natural abundance of sulfur nuclides.

REFERENCES.

1) For reviews, see: (a) Curci, R. in Advances in Oxygenated Processes; Baumstark, A.L. Ed.; JAI: Greenwich, CT, 1990; Vol. 2, Chapter I, pp. 1-59. b) Adam, W.; Curci, R.; Edwards, J.O. Acc. Chem. Res. **1989**, 22, 205. c) Murray, R.W. Chem. Rev. **1989**, 89, 1187.

2) a) Edwards, J.O.; Pater, R.H.; Curci, R.; Di Furia, F. Photochem. Photobiol. **1979**, 30, 63. b) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J.O.; Pater, R.H. J. Org. Chem. **1980**, 45, 4758. c) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. J. Org. Chem. **1982**, 47, 2670. d) Curci, R.; Fiorentino, M.; Serio, M.R. J.Chem.Soc.Chem. Commun. **1984**, 155.

3) Jeyaraman, R.; Murray, R.W., J. Am. Chem. Soc., **1984**, 106, 2462.

4) Murray, R.W.; Jeyaraman, R. J. Org. Chem., **1985**, 50, 2847.

5) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci R. J. Org. Chem. **1988**, 53, 3890.

6) Murray, R.W.; Jeyaraman, R.; Mohan, L. J. Am. Chem. Soc., **1986**, 108, 2470.

7) a) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. J. Am. Chem. Soc., **1989**, 111, 6749. b) Mello, R.; Cassidei, L.; Fiorentino, M.; Fusco, C.; Curci, R. Tetrahedron Lett. **1990**, 31, 3067.

8) Adam, W.; Mello, R.; Curci, R., Angew. Chem. Int. Ed. Engl. **1990**, 29, 890.

9) a) Troisi, L.; Cassidei, L.; Lopez, L.; Mello, R.; Curci, R. Tetrahedron Lett., **1989**, 30, 257.Baertschi, S.W.; Raney, K.D.; Stone, M.P.; Harris, T.M. J. Am. Chem. Soc. **1988**, 110, 7929.

10) Adam, W.; Hadjiarapoglou, L.; Jäger, V.; Seidel, B. Tetrahedron Lett. **1989**, 30, 4223.

11) Crandall, J.K.; Batal, D.J., J. Org. Chem., **1988**, 53, 1338.

12) a) Halcomb, R.L.; Danishefsky, S.J., J. Am. Chem. Soc., **1989**, 111, 6661. b) Chow, K.; Danishefsky, S. J. Org. Chem. **1990**, 55, 4211.

13) Murray, R.W.; Jeyaraman, R.; Pillay, M.K.; J. Org. Chem., **1987**, 52, 746.

14) Quallich, G.J.; Lackey, J.W., Tetrahedron Lett., **1990**, 31, 3685.

15) Evans, T.L.; Grade, M.M., Synthetic Comm., **1986**, 16, 1207.

16) Trost, B.M.; Curran, D.P., Tetrahedron Lett., **1981**, 22, 1287.

17) Adam, W.; Chan, Y.Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M.; J. Org. Chem. **1987**, 52, 2800.

18) Colonna, S.; Gaggero, N., Tetrahedron Lett., **1989**, 30, 6233.

19) Sugimoto, T.; Kokobu, T.; Miyasaki, J.; Tanimoto, S.; Okano, M., Biorg. Chem., **1981**, 10, 311.

20) Chiari, M.; Righetti, P.G.; Colonna, S.; Gaggero, N.; Negri, A., Electrophoresis, in press.

21) Eliel, E.L.; Ro, R.S., J. Am. Chem. Soc., **1957**, 79, 5995.

22) Shriner, R.L.; Struck, H.C.; Jorison, W.L., J. Am. Chem. Soc., **1930**, 52, 2060.

23) Gilman, H.; King, W.B.; J. Am. Chem. Soc., **1925**, 47, 1136.

24) Newell, O.; Calaway, P.K., J. Am. Chem. Soc., **1947**, 69, 116.

25) Delisle, A., Ann., 1890, 260, 250.

26) Bedell, S.F.; Spaeth, E.C.; Bobbitt, J.M. J. Org. Chem., **1962**, 27, 2026.

27) Colonna, S.; Banfi, S.; Fontana, F.; Sommaruga, M., J. Org. Chem., **1985**, 50, 769.

28) Long, L.M. J. Am. Chem. Soc., **1946**, 68, 2159.

29) Komori, T.; Nonaka, T., J. Am. Chem. Soc., **1984**, 106, 2656.

30) Auret, B.J.; Boyd, D.R.; Henbest, H.B.; Ross, S. J. Chem. Soc. (C), **1968**, 2371.

31) Pitchen, P.; Dunach, E.; Deshmukh, M.N.; Kagan, H.B.; J. Am. Chem. Soc., **1984**, 106, 8188.

32) Kunieda, N.; Suzuki, A.; Kinoshita, M.; Bull. Chem. Soc. Jpn., **1981**, 54, 1143.

33) Leatherbavrow, R.S. in "Enzfitter a non-linear regression data analysis program for I.B.M. P.C.", Elsevier BIOSOFT, Cambridge, 1987.