separated. The usual workup gave **methyl 2,3-dimethyl-2-hydroxy-4-pentynoate**: ^{1}H NMR (CCl_4) δ [erythro isomer] 1.12 (3 H, d, J = 7.5 Hz), 1.44 (3 H, s), 2.01 (1 H, m), 2.75 (1 H, q, J = 7.5 Hz), 3.03 (1 H, br), 3.78 (3 H, s), [threo isomer] 1.19 (3 H, d, J = 7.5 Hz), 1.35 (3 H, s), 2.01 (1 H, m), 2.76 (1 H, q, J = 7.5 Hz), 3.03 (1 H, br), 3.71 (3 H, s); IR (CCl_4, cm^{-1}) 1720, 2150, 3500; exact mass calcd for $C_8H_{12}O_3$ m/z 156.0786, found m/z 156.0777. The R group of **19** and **20** was converted to Me group during the desilylation step. The acetylenic ester was reduced with Lindler catalyst. To a solution of 20 mg of Pd–$BaSO_4$ dissolved in 5 mL of MeOH was added the ester (0.5 mmol) in MeOH. The usual hydrogenation gave **5** and **6** (R = Me).

Enantio- and Diastereoselectivity in the Periodate Oxidation of Sulfides Catalyzed by Bovine Serum Albumin. 2[1]

Stefano Colonna,* Stefano Banfi, and Rita Annunziata

Centro CNR and Dipartimento di Chimica Organica e Industriale dell'Università, 20133 Milano, Italy

Luigi Casella

Centro CNR and Dipartimento di Chimica Inorganica e Metallorganica dell'Università, 20133 Milano, Italy

Received June 25, 1985

The asymmetric oxidation of aliphatic, aromatic, and heterocyclic sulfides in the presence of a catalytic amount of bovine serum albumin (BSA) affords the corresponding sulfoxides with enantiomeric excess (ee) up to 80%. The diastereoselectivity of the process has also been examined in comparison with the enzymatic oxygenation with cytochrome P-450. Electronic and CD spectral data indicate that the sulfides are not tightly bound to BSA in the reaction conditions.

Natural and synthetic polypeptides have been recently used to promote asymmetric induction. In spite of the increasing availability of enzymes as chiral catalysts, nonenzymic catalytic asymmetric synthesis is still a powerful tool in organic chemistry. Almost enantioselective reactions have been performed, inter alia, in the cyanohydrin synthesis catalyzed by a synthetic cyclic dipeptide[2] and in the epoxidation of electron-poor olefins in the presence of poly(α-amino acids).[3]

On the other hand, natural globular proteins, which also present a chiral environment, have the unique property of specific binding sites for hydrophobic organic molecules. They are available in large quantity in a optically pure form, and this constitutes a big advantage with respect to synthetic polypeptides. Outstanding results have been reported by Whitesides[4] and Sugimoto[5] in the asymmetric hydrogenation of 2-acetamidoacrylic acid with a modified avidin and in the stereoselective oxidation of aromatic sulfides catalyzed by bovine serum albumin (BSA), respectively.

More recently the versatility of BSA as chiral catalyst has been emphasized by the enantioselective hydroxylation of alkenes[6] and in the Darzens condensation.[7]

Previously, we have shown that the asymmetric periodate oxidation of functionalized sulfides with BSA proceeds smoothly to give the corresponding sulfoxide with satisfactory optical purity.[1] In order to verify the generality of this type of asymmetric synthesis, we have now investigated the metaperiodate oxidation of aliphatic, aromatic, and heterocyclic sulfides. Furthermore it was interesting to establish the diastereoselectivity of the reaction and to compare it to that of enzymatic oxygenation with cytochrome P-450.[8]

The effect on the stereoselectivity of a number of variables such as (i) pH, (ii) the nature of the oxidizing agent, and (iii) the addition of denaturing agents has also been studied.

In this context it must be stressed that there are still several uncertainties in the understanding of the mechanism responsible for these asymmetric syntheses. An investigation of the electronic and CD spectra of BSA in the presence of the sulfides and the oxidizing agent was therefore undertaken to the end of establishing whether substrate binding to the protein occurs in the conditions employed for the catalytic oxidations.

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 in a buffer solution (0.05 mol). In ancillary experiments with sulfides **4** and **10** we found that the use of lower amounts of BSA (0.02 mol) slowed down the reaction rate, affording the corresponding sulfoxides **18** and **24**, respectively, with comparable or lower enantioselectivity. On the other hand the use of a higher amount of BSA (0.1 mol) resulted in an increase of the chemical yields but in a lowering of the stereoselectivity.[1]

$$\underset{\textbf{1-14}}{RSR'} \xrightarrow[\text{BSA}]{\text{aqueous } NaIO_4} \underset{\textbf{15-28}}{RS^*(=O)R'}$$

The sulfides used were *tert*-butyl *n*-butyl sulfide (**1**), dodecyl methyl sulfide (**2**), mesityl phenyl sulfide (**3**), bis(*p*-tolylthio)methane (**4**), 1,3-dithiane (**5**), 2-methyl-2,3-dihydrobenzothiophene (**6**), 1-thiochroman (**7**), 2-methyl-1-thiochroman (**8**), *sec*-butyl *p*-tolyl sulfide (**9**),

(1) Colonna, S.; Banfi, S.; Fontana, F.; Sommaruga, M. *J. Org. Chem.* **1985**, *50*, 769.
(2) Oku, J.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1981**, 229.
(3) (a) Banfi, S.; Colonna, S.; Molinari, H.; Juliá, S.; Guixer, J. *Tetrahedron* **1984**, *40*, 5207 and references therein. (b) Comprehensive reviews on asymmetric reactions catalyzed by synthetic polypeptides appear in: Inoue, S. *Adv. Polym. Sci.* **1976**, *21*, 78. Martens, J. *Top. Curr. Chem.* **1984**, *125*, 167.
(4) Whitesides, G. M.; Wilson, M. E. *J. Am. Chem. Soc.* **1978**, *100*, 306.
(5) Sugimoto, T.; Kokobu, T.; Miyasaki, J.; Tanimoto, S.; Okano, M. *Bioorg. Chem.* **1981**, *10*, 301.
(6) Kokobu, T.; Sugimoto, T.; Uchida, T.; Tanimoto, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1983**, 769.
(7) Annunziata, R.; Banfi, S.; Colonna, S. *Tetrahedron Lett.* **1985**, *26*, 2471.
(8) Takata, T.; Yamazaki, M.; Fujimori, K.; Kim, Y. H.; Iyanagi, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2300.

0022-3263/86/1951-0891$01.50/0

Table I. Oxidation of Sulfides 1–5, 7, 10, and 12–14 with $NaIO_4$ in a Buffer Solution Containing BSA at 25 °C

cmpd	pH	reacn time, h	yield, %	$[\alpha]_D$, deg	ee,[b,j] %
1	9	4	33	+36[a]	29
1	7	4	36	+41[a]	33
1	5	4	64	+30[a]	24
2	9	4	38	+6[c]	
3	9	4	8	+35[a]	40
4[d]	9	15	19	+29[a]	38
4[d]	5	15	13	+20[a]	26.5
5	9	4	25	+8[e]	3
5	7	4	37	+10.5	4.5
7	9	4	70	−55[a]	27
10	9	4	60	+103[e]	69
10	7	4	26	+75[e]	51
10	11	4	77	+69[e]	49
10[f]	9	4	70	+90[e]	60
10[g]	9	4	60	+89[e]	59
12	9	4	58	−121[a]	42
13	9	72	19	+5	
14	9	17	20	+63[h]	80
14	9	17	12	+19[i]	

[a] In acetone as solvent. [b] Determined by ^1H NMR with $Eu(hfc)_3$ as chiral shift reagent. [c] In chloroform as solvent. [d] For the reaction conditions see the Experimental Section. [e] In ethanol as solvent. [f] With defatted BSA. [g] In the presence of 8 M urea. [h] Threo diastereoisomer.[22] [i] Erythro diastereoisomer.[22] [j] The kinetic resolution accompanying the asymmetric oxidation is negligible.

tert-butyl 1-(*p*-tolylthio)acetate (**10**), *tert*-butyl 1-[(*p*-nitrophenyl)thio]acetate (**11**), dihydrobenzothiophene (**12**), *p*-nitrophenyl phenyl sulfide (**13**), and 1-phenyl-2-(phenylthio)ethanol **14**. The ee's were determined by ^1H NMR spectroscopy with $Eu(hfc)_3$ as chiral shift reagent.

Results and Discussion

The data relative to the enantioselectivity in the oxidation of sulfides **1–6**, **10**, and **12–16** with $NaIO_4$ and BSA collected in Table I lead to the following conclusions:

(i) In all cases examined optically active sulfoxides are obtained, independently, on the structural features of the starting sulfide, although in the case of 1,3-dithiane (**5**) the reaction product is almost racemic.

(ii) The highest ee's are obtained with 2-(phenylsulfinyl)ethanol (**28a**), one of the two possible diastereoisomers, and with *tert*-butyl 1-(*p*-tolylsulfinyl)acetate (**24**), 80% and 69.0% ee, respectively.

(iii) There exists an absence of a noticeable pH dependence of stereoselectivity in the range 5–11 for a representative dialiphatic (**1**), diaromatic (**4**), and heterocyclic (**5**) sulfides.

(iv) Starting from 1-thiochroman (**7**) the oxidation with $NaIO_4$ and BSA affords the (−)-(*S*)-sulfoxide. Its absolute configuration is the same of the prevailing enantiomer obtained by Oae[8] using the cytochrome P-450, but its enantiomeric purity is twice as great.

(v) The increase of the enantioselectivity on passing from the cytochrome P-450 to the $NaIO_4$–BSA system is much more significant in the oxidation of dihydrobenzothiophene (**12**). The (−)-(R)-sulfoxide **26** is obtained in both cases, the enantiomeric excesses being 2.6% and 42%, respectively.

(vi) The addition of urea, a typical denaturing agent, does not substantially alter the degree of enantioselectivity.

We have also examined the diastereoselectivity in the oxidation of sulfides, having a stereocenter, in the presence of BSA and $NaIO_4$ or *m*-chloroperbenzoic acid (MCPBA) as oxidizing agents (Table II and last entry of Table I).

For compounds **6** and **8**, the results may be compared to those observed either in the enzymatic oxidation with cytochrome P-450 or in the absence of the chiral catalyst

Table II. Diastereoselectivity in the Oxidation of Sulfides 6, 8, and 9 in a Buffer Solution Containing BSA at 25 °C

cmpd	pH	oxidant	reacn time, h	yield, %	diastereomeric ratio[a]
6	9	$NaIO_4$	4	35	26:74[b]
6	9	MCPBA	4	38	47:53[c]
8	9	$NaIO_4$	5	90	67:33[d]
8	9	MCPBA	48	22	66:34[d]
9	9	$NaIO_4$	89	5	62:38[e]
9	9	MCPBA	31	41	50:50[c]

[a] Cis–trans ratio. [b] ee of the cis sulfoxide was 33% and ee of the trans sulfoxide was 18%, as determined by ^1H NMR with $Eu(hfc)_3$ as chiral shift reagent. [c] Racemic mixture. [d] Enantiomeric excess not determined. [e] The major diastereoisomer, having *RS* absolute configuration, has 28% ee; the minor diastereoisomer, having *RR* absolute configuration, has 44% ee as determined by ^1H NMR with $Eu(hfc)_3$ as chiral shift reagent.

Table III. Diastereoselective Enzymatic and Nonenzymatic Oxidation of Sulfides 6 and 8 at 37 °C for 1.5 h[a]

cmpd	protein	oxidant	cis:trans ratio
6	yes		19:81
6		MCPBA	47:53
6		$NaIO_4$	48:52
8	yes		18:82
8		MCPBA	56:44
8		$NaIO_4$	55:45

[a] All data are from ref 8.

(Table III). Nonenzymic oxidation with MCPBA and $NaIO_4$ gives almost the same cis/trans ratio both with 2-methyl-2,3-dihydrobenzothiophene (**6**) and 2-methyl-1-thiochroman (**8**).

By contrast $NaIO_4$ in the presence of BSA and cytochrome P-450 favors the formation of the trans diastereoisomer, starting from the former compound.

The influence of the protein on the diastereoselectivity is less relevant in the metaperiodate oxidation of 2-methyl-1-thiochroman (**8**), which leads to sulfoxides **22a** and **22b** in a 63:37 ratio. In this case the prevailing diastereoisomer, namely the cis, has the opposite configuration of that obtained in the enzymic oxidation.

The preferential formation of the trans isomer using cytochrome P-450 on cyclic sulfides has been rationalized by Oae on the basis of an electrophilic attack on sulfur, by the large oxenoid porphyrin system of the cytochrome, from the less hindered side. On the other hand, the opposite diastereoselectivities met with in the oxidation of the two cyclic sulfides **6** and **8** with $NaIO_4$ and BSA is not surprising; indeed also the sense of enantioselectivity is influenced by minimal structural variations of the substrates.[5]

Finally it should be pointed out, once again, the more pronounced diastereoselectivity of $NaIO_4$ with respect to MCPBA in the oxidation of *sec*-butyl *p*-tolyl sulfide (**9**) with BSA.

We want also to report here the different behavior of the human (HSA) and bovine serum albumin in the metaperiodate oxidation of our standard sulfide, namely the *tert*-butyl 1-(*p*-tolylthio)acetate (**10**); the two proteins give the (−)-(S)- and the (+)-(*R*)-sulfoxides **24**, with 1.2% and 69.3% ee, respectively.

Human and bovine serum albumin are composed in a similar manner. They are homologous in their domain and subdomains and in the pattern of the disulfide bridges; their α-helix content is very similar (75% or more). However, the sequences of the amino acids of the two proteins are not identical.

Although the majority of ligands are binded to the two albumins equally well, there are some exceptions. Wolley

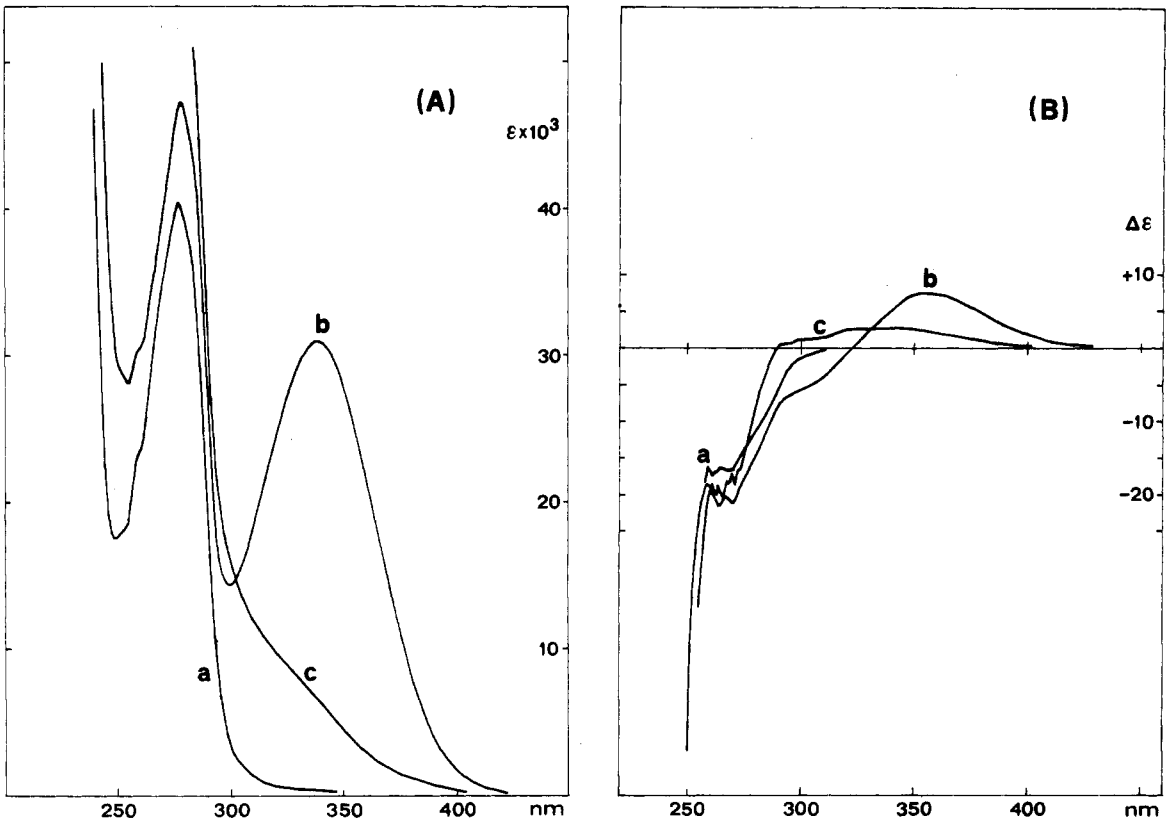


Figure 1. Electronic (A) and circular dichroism (B) spectra of (a) bovine serum albumin in water, (b) the mixture BSA and *tert*-butyl [(*p*-nitrophenyl)thio]acetate (1:20) in water after centrifugation, and (c) the mixture BSA/*tert*-butyl [(*p*-nitrophenyl)thio]acetate/$NaIO_4$ (1:20:40) after centrifugation within a few minutes of the addition of the oxidant.

and Hunter observed[9] opposite Cotton effects in the circular dichroism spectra of bilirubin binded to human and bovine serum albumin. These are explained by different conformation of the primary substrate binding sites of the two proteins. It could equally well account for the opposite stereochemistry of the metaperiodate oxidation of sulfide **10**.

Information on the adducts formed by bovine serum albumin with the sulfides in the reaction conditions can in principle be obtained by the CD spectra of the mixtures. In order to observe the CD features and evolution of protein/substrate complexes during the catalytic oxidations it was necessary to use sulfides, such as **11** and **13**, containing *p*-nitrophenyl sulfide chromophores, which absorb at wavelengths bathochromically shifted with respect to the intense near-UV electronic and CD absorptions of the aromatic residues of BSA and undergoing oxidation reactions at very low rate. The near-UV CD spectrum of BSA is characterized by a broad negative band near 280 nm that is only partially resolved from the intense, negative protein CD band at higher energy (Figure 1). The addition of a large excess of *tert*-butyl 1-(*p*-nitrophenyl)thio]acetate or *p*-nitrophenyl phenyl sulfide to BSA in aqueous borate buffer (pH 9) produces the appearance of well-defined CD activity between 300 and 400 nm in the solution obtained after centrifugation; this corresponds to the low-energy absorptions of the sulfides (near 340 nm) but is outside the range spanned by the protein absorptions (Figure 1). A rough estimate of the number of sulfide molecules per molecule of BSA can be obtained from the ratio of intensity of the absorption bands near 340 nm (due to the sulfide) and near 280 nm (contributed both by the sulfide and BSA) using molar extinction coefficients of the sulfides determined in ethanol solution. This gives an approximate molar ratio of **11**/BSA equal to 3.5 and **13**/BSA equal to 2 in the aqueous buffer solution. Since the sulfides are practically insoluble in water it can be considered that these substrates become dissolved in the aqueous medium on binding to BSA. The formation of BSA/sulfide complexes is confirmed by the induction of CD activity within the electronic transitions of the achiral sulfide chromophores. Such induced Cotton effects are probably originated by coupling of the low-energy $\pi-\pi^*$ transitions of the *p*-nitrophenyl sulfide chromophores with intense transitions of the same type localized within aromatic residues of the protein that are relatively close to but asymmetrically disposed around the substrate molecules. An alternative explanation for the origin of the CD activity above 300 nm based on its localization on conformationally modified disulfide bridges of the protein[10] can be discarded because such CD activity is not observed in the spectra of BSA/substrate mixtures containing sulfides adsorbing at higher energy.

Somewhat surprising was initially the results that the addition of a large excess of oxidizing agent (relative to BSA or BSA/sulfide complexes) causes an immediate displacement of the sulfides from the binding sites of the protein. This is clearly evidenced by the electronic and CD spectra recorded on the mixtures BSA/**11**/$NaIO_4$ or BSA/**13**/$NaIO_4$. In the absorption spectra a broad shoulder in the range 300–340 nm, at least partly due to $NaIO_4$, replaces the much more intense absorption band near 340 nm of the BSA/*p*-nitrophenyl sulfide complexes, while only weak and featureless CD activity of positive sign occurs above 300 nm (Figure 1). While the presence of very

(9) Wolley, P. V.; Hunter, M. J. *Arch. Biochem. Biophys.* **1970**, *140*, 197.

(10) Mason, S. F. "Molecular Optical Activity and the Chiral Discrimination"; Cambridge University Press: Cambridge, 1982; Chapter 5.

low amounts of sulfides bound to BSA cannot be excluded, the spectral features of the ternary systems of BSA/*p*-nitrophenyl sulfide/$NaIO_4$ are basically determined by a conformational modification of BSA in the presence of the large excess of oxidizing agent. Very similar electronic and CD spectra were in fact obtained for binary mixtures of BSA/$NaIO_4$ or BSA/MCPBA in the same conditions (molar ratio of BSA/oxidizing agent, 1/40). Since the electronic and CD spectra of BSA are essentially unaffected by the addition of low amounts of $NaIO_4$ or MCPBA (ratio of BSA/oxidizing agent, ~1/5), we believe that the broad CD activity above 300 nm originates within the disulfide chromophores of conformationally modified cystine bridges of the protein,[11] rather than transitions within molecules of $NaIO_4$ or MCPBA bound to BSA. Finally, it should be mentioned that some further minor changes in the CD spectra of the systems BSA/*p*-nitrophenyl sulfide/$NaIO_4$ can be observed during the course of the oxidation reaction; these are at least partly due to the formation of the chiral sulfoxides but may also result from some slow oxidation reaction undergone by residues of the protein in the presence of the oxidizing agent.

Conclusions

The metaperiodate oxidation of aliphatic, aromatic, and heterocyclic sulfides confirms our previous results.[1] The use of a catalytic amount of protein in all cases gives rise to asymmetric synthesis. The absence of a significant dependence of the enantioselectivity on the pH in the range 5–11 is verified for substrates having very different structures. This is in contrast with the dramatic decrease in the optical purity of the reaction products below pH 8 observed by Sugimoto.[5]

However, it must be stressed that the experimental conditions are quite different in the two cases; inter alia, the substrate–protein ratios are 20:1 and 3:1, respectively. As a tentative explanation for this dichotomic behavior of the bovine serum albumin we have already postulated the intervention of a larger number of nonspecific binding sites in our catalytic oxidations (~20 instead of the three specific proposed by Sugimoto).

The present CD results show that migration of the substrate from the specific binding sites to nonspecific binding sites is determined by the addition of large amounts of oxidizing agent to the mixture BSA/substrate. Indeed, the UV spectral changes in such conditions are more indicative of expulsion of the sulfides from the specific binding sites as a result of dramatic conformational change of the protein. Nonspecific binding of the sulfides does not necessarily involve strong and permanent BSA/substrate interactions; this could account for the relatively low amounts of sulfides that seem likely present in the mixtures BSA/$NaIO_4$/substrate. The conformational modification of BSA induced by $NaIO_4$ or MCPBA may involve a partial denaturation of the protein, since the presence of urea in the oxidation of sulfide **10** does not affect markedly the enantioselectivity of the reaction. This is in line with the observation that the presence of sodium lauryl sulfate in the same reaction conditions gives only optically inactive sulfoxide **20**. We note that low ratios of $NaIO_4$/BSA (≤5:1) do not apparently produce a significant modification of the protein. Therefore it is likely that in the almost stoichiometric conditions employed by Sugimoto the addition of the oxidizing agent causes only minor conformational changes of BSA and hence negligible substrate expulsion from the specific binding sites.

(11) BSA contains 17 cystine disulfide bridges per molecule.

The different ligand protein interaction in the case of HSA and BSA could be used as a tool for asymmetric syntheses promoted by the two globular proteins.

Not only the enantioselectivity but also the diastereoselectivity in the periodate oxidation of sulfides is affected by the presence of bovine serum albumin. The nonspecific hydrophobic interactions between the substrate and the protein are reminiscent of enzymic systems. They determine the microscopic chiral environment of the reaction and favor the localization of the sulfide on the globular protein.

The higher optical purities of sulfoxides **21** and **26** obtained with $NaIO_4$ and BSA instead of cytochrome P-450 also deserves a comment. This enzyme, whose crucial role is the oxidation of xenobiotics in the liver, is characterized by a low substrate specificity and stereospecificity in comparison with most other monooxygenases. Dopamine β-hydroxylase[12] and flavoenzymes monooxygenases[13] are the enzymes of choice for the oxidation of sulfides to the corresponding sulfoxides.

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 part per million (δ) relative to internal Me_4Si on a Varian 390 instrument. Enantiomeric excesses were determined by ^1H NMR with the aid of $Eu(hfc)_6$ as shift reagent by using a Varian XL 200 instrument. The CD spectra were recorded on a Jobin Yvonne Mark III dichrograph calibrated with a solution of isoandrosterone in dioxane. The UV spectra were recorded on a Varian CARY 219 instrument. BSA was the fraction V Fluka commercial product.

Preparation of Sulfides 1–14. 1,3-Dithiane (**5**) was a Fluka commercial product. Compounds **1–4**, **6–10**, **12**, and **13** were prepared according to the literature, and their physical properties were in agreement with those reported.

Compound **14**, prepared following the method of Corey and Seebach[14] by reaction of [(phenylthio)methyl]lithium and benzaldehyde, was obtained in 91% yield, bp 180 °C (1.5 mm), n_D^{27} 1.6109 [lit.[14] bp 156 °C (0.04 mm)].

***tert*-Butyl 1-[(*p*-Nitrophenyl)thio]acetate (11).** Compound **11** was prepared according to the method of Newell and Calaway[15] by reaction of the thiolate and the properly functionalized alkyl halide. It was obtained in 80% yield: mp 47–49 °C; ^1H NMR δ 1.4 (s, 9 H), 3.65 (s, 2 H), 7.4 (d, 2 H), 8.1 (d, 2 H). Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.5; H, 5.6; N, 5.2. Found C, 53.3; H, 5.7; N, 5.3.

Oxidation: 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 the appropriate time (see Tables I and II). Extraction with four portions (60 mL each) of diethyl ether and evaporation of the organic layer after drying gave the crude product, which was purified by chromatography on silica gel with mixtures of ether and petrol as eluant. The yields and the optical rotation values are reported in Tables I and II.

Oxidation: Procedure Used for Substrate 4. The sulfide (1 mmol) and 1.32 g of BSA (2×10^{-2} mmol) were magnetically stirred in 50 mL of buffer solution for 2 h at 20 °C, then $NaIO_4$ (2 mmol) was added, and the mixture was kept stirring for 15 h. The workup as described above gave the corresponding sulfoxide (see Table I).

Characteristics of the Sulfoxides. *tert*-Butyl *n*-butyl sulfoxide (**15**),[16] (*p*-tolylsulfinyl)(*p*-tolylthio)methane (**18**),[17] 1,3-

(12) May, S. W.; Phillips, R. S.; Mueller, P. W.; Herman, H. H. *J. Biol. Chem.* **1981**, *256*, 8470.
(13) Light, D. R.; Waxman, D. J.; Walsh, C. *Biochemistry* **1982**, *21*, 2490.
(14) (a) Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097. (b) Kaufmann, H. P.; Schickel, R. *Fette, Seifen, Austrichm.* **1963**, *65*, 851; *Chem. Abstr. 60*, 10583*f*.
(15) Newell, O.; Calaway, P. K. *J. Am. Chem. Soc.* **1947**, *69*, 116.

dithiane 1-oxide (19),[18] 2-methyl-2,3-dihydrobenzothiophene 1-oxide (20),[8] thiochroman 1-oxide (21),[8] 2-methyl-1-thiochroman 1-oxide (22),[8] *sec*-butyl *p*-tolyl sulfoxide (23),[19] *tert*-butyl 1-(*p*-tolylsulfinyl)acetate (24),[1] and 2,3-dihydrobenzothiophene 1-oxide (26)[8] were all known in the optically active form, and the physical properties of our specimens were in agreement with those reported. Yields and optical rotation are reported in Tables I and II.

Sulfoxides 16, 27, and 28 were known in the racemic form. 1-(Methylsulfinyl)dodecane (16) had mp 53 °C (lit.[20] mp, 59–61 °C): ^{1}H NMR δ 0.9 (brt, 3 H), 1.1–1.9 (m, 20 H), 2.55 (s, 3 H), 2.65 (dt, 2 H).

1-Nitro-4-(phenylsulfinyl)benzene (27) had mp 100–101 °C (lit.[21] mp 107–107.5 °C): ^{1}H NMR δ 7.4–7.7 (m, 5 H), 7.8 (d, 2 H), 8.3 (d, 2 H).

2-(Phenylsulfinyl)-1-phenyl-1-ethanol (28).[22] Only the threo isomer having the major R_f has been isolated by flash chromatrography on silica gel, using petrol/ether (9/1) as eluant. It had mp 115–118 °C; ^{1}H NMR δ 2.8 (dd, 1 H), 3.15 (dd, 1 H), 4.05 (brs, 1 H), 5.3 (dd, 1 H), 7.2–7.7 (m, 10 H). The erythro isomer, isolated as a mixture with the threo diastereoisomer, had the following: ^{1}H NMR δ 2.9 (dd, 1 H), 3.2 (dd, 1 H), 4.2 (brs, 1 H), 5.15 (brd, 1 H), 7.2–7.7 (m, 10 H).

2,4,6-Trimethyl-1-(phenylsulfinyl)benzene (17) was a wax: ^{1}H NMR δ 2.25 (s, 3 H), 2.40 (s, 6 H), 6.85 (s, 2 H), 7.4 (m, 5 H). Anal. Calcd for $C_{15}H_{16}OS$: C, 73.8; H, 6.5. Found C, 73.5; H, 6.4.

***tert*-Butyl 1-[(*p*-nitrophenyl)sulfinyl]acetate (25)** had mp 137–139 °C; H NMR δ 1.5 (s, 9 H), 3.8 (t, 2 H), 7.9 (d, 2 H), 8.4 (d, 2 H). Anal. Calcd for $C_{12}H_{15}NO_5S$: C, 50.5; H, 5.3; N, 4.9. Found C, 50.1; H, 5.5; N, 4.8.

Preparation of the Solutions of BSA/*p*-Nitrophenyl Sulfides for Electronic and CD Spectral Measurements. Electronic and CD spectra of binary mixtures of BSA/11 or BSA/13 were recorded on solutions prepared according to the following procedure. The sulfide (1 mmol) and BSA (5×10^{-2} mmol) were magnetically stirred in aqueous borate buffer solution at pH 9 (12.5 mL) at room temperature. After 2 h a sample of the mixture (2 mL) was withdrawn and centrifugated at 20000 rpm for 15 min (36 000 g). The resulting clear solution (0.5 mL) was diluted with water as needed for the observation of the electronic and CD spectra. The spectra of ternary mixtures of BSA/*p*-nitrophenyl sulfide/oxidizing agent were obtained from samples withdrawn at different times after the addition of the oxidizing agent to the mixture BSA/sulfide and treated as above.

(16) Lockard, J. P.; Schoeck, C. W.; Johnson, C. R. *Synthesis*, **1973**, 485.
(17) Ogura, K.; Fujita, M.; Iida, H. *Tetrahedron Lett.* **1980**, *21*, 2233.
(18) Auret, B. J.; Boyd, D. R.; Cassidy, E. S.; Turley, F.; Drake, A. F.; Mason, S. *J. Chem. Soc., Chem. Commun.* **1983**, 282.
(19) Annunziata, R.; Cinquini, M.; Colonna, S.; Cozzi, F. *J. Chem. Soc., Chem. Commun.* **1981**, 1005.
(20) Langhlin, R. G. *J. Org. Chem.* **1960**, *25*, 864.
(21) Szmant, H. H.; McIntosh, J. J. *J. Am. Chem. Soc.* **1951**, *73*, 4356.
(22) Kingsbury, C. A.; Auerbach, R. A. *J. Org. Chem.* **1971**, *36*, 1737.

Hydroboration. 77. Revision of the Regioselectivity of the Hydroboration of Alkenes with Dihaloborane–Dimethyl Sulfide Complexes

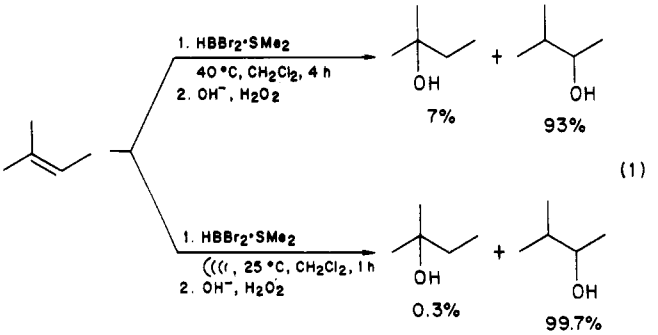
Herbert C. Brown* and Uday S. Racherla

Richard B. Wetherill Laboratory, Purdue University, West Lafayette, Indiana 47907

Received August 14, 1985

The hydroboration of alkenes with dihaloborane–dimethyl sulfide complexes ($HBX_2{\cdot}SMe_2$, X = Cl, Br, and I) was systematically reexamined to establish the true regioselectivities in hydroboration with these reagents. Hydrogen halides (HX, X = Cl, Br, and I) liberated during the hydrolysis–oxidation of the alkyldihaloborane–dimethyl sulfide complexes ($RBX_2{\cdot}SMe_2$) add to the residual alkene and hydrolyze to alcohols, thus introducing a significant error in the regioselectivity of such hydroborations. The true regioselectivities in the hydroboration of alkenes with $HBX_2{\cdot}SMe_2$ reveal considerably smaller formation of secondary and tertiary derivatives than previously reported, a result that should significantly enhance the value of these hydroborating agents.

Recently we reported that ultrasound remarkably improves the rates of heterogeneous hydroborations and has a modest accelerating influence on the rates of homogeneous hydroborations.[1] In the course of these studies, we unexpectedly discovered remarkable changes in the regioselectivities of hydroboration of certain alkenes with $HBBr_2{\cdot}SMe_2$. For example, while the hydroboration of 2-methyl-2-butene with $HBBr_2{\cdot}SMe_2$ under the usual conditions (40 °C, CH_2Cl_2, 4 h) followed by hydrolysis–oxidation affords[2] 7% of 2-methyl-2-butanol and 93% of 3-methyl-2-butanol, the same hydroboration done under ultrasound conditions ((((, 25 °C, CH_2Cl_2, 1 h) gave after oxidation 0.3% of 2-methyl-2-butanol and 99.7% of 3-methyl-2-butanol (eq 1).



(1)

Intrigued by this change, we decided to reexamine the hydroboration of 2-methyl-2-butene with $HBBr_2{\cdot}SMe_2$ at 25 °C in CH_2Cl_2 (in the absence of ultrasound). Accordingly, we followed the hydroboration with time by hydrolyzing and oxidizing aliquots (withdrawn at regular intervals of time) and analyzing the alcohols by GC.

(1) Brown, H. C.; Racherla, U. S. *Tetrahedron Lett.* **1985**, *26*, 2187.
(2) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1980**, *45*, 384.

0022-3263/86/1951-0895$01.50/0