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Stereoselective Oxidation of Aromatic Sulfides and Sulfoxides in the Binding Domain of Bovine Serum Albumin

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The oxidation of aromatic sulfides with achiral oxidizing agents, e.g., sodium metaperiodate ($NaIO_4$) and hydrogen peroxide (H_2O_2) in the binding domain of bovine serum albumin (BSA), furnished a strong asymmetric bias (max 81%) of the product sulfoxides in fairly high chemical yields. The kinetic resolution of racemic aromatic sulfoxides was also carried out in the chiral binding domain, and the remaining unchanged sulfoxides showed optical purities ranging over 1–33% at ca. 50% completion of oxidation. The combination of the two stereoselective oxidations above mentioned produced several optically active sulfoxides of >90% optical purity in ca. 50% chemical yield. The present method constitutes a successful biomimetic approach to achieving stereoselectivities as high as obtained by sulfur-oxidizing microorganisms.

INTRODUCTION

We have previously demonstrated that the binding domain of BSA serves as a chiral template for producing optically active aromatic alcohols of high optical purity (max 78%) in the reduction of the ketones with achiral reducing agents such as sodium borohydride (*1*), sodium cyanoborohydride (*1*), and an NADH model compound (*2*). This provides the first successful biomimetic approach involving highly stereoselective reactions conducted in a chiral environment of binding sites similar to enzyme active sites (*3*). Nevertheless, familiar chemical methods using chiral reducing agents in general achieve higher stereoselectivity in the asymmetric reduction of carbonyl compounds (*4*), thereby leaving less synthetic utility to the above method. In our attempts to establish the usefulness of this method in asymmetric synthesis we sought asymmetric reactions in which high stereoselectivity can not be readily obtained by methods using chiral agents. Asymmetric oxidation of aromatic sulfides (**1**) and sulfoxides (**2**) was chosen as a most suitable reaction. The present paper gives details of the stereoselective oxidation of **1** (step a) and kinetic resolution of racemic **2** (step b) in the binding domain of BSA (Scheme 1) (*5*). We have also studied the two-stage oxidation of **1**, i.e., the continuous oxidation of **1** involving steps a and b, and succeeded in the preparation of optically active **2** of >90% optical purity, as obtained by sulfur-oxidizing microorganisms of *Aspergillus niger*, *Rhizopus arrhizus*, and *Rhizopus stolonifer*, etc. (*6*).

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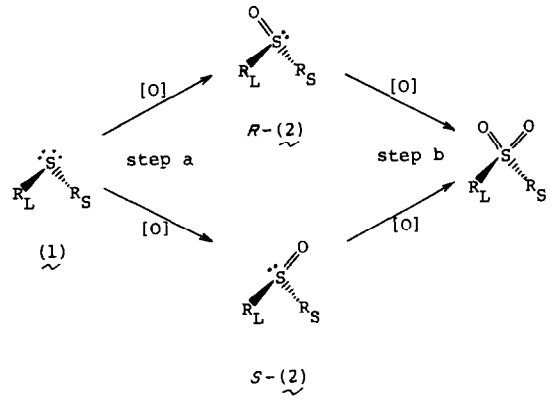


RESULTS

Stereoselective Oxidation of **1** *in the Binding Domain of BSA*

The oxidation of **1** with an achiral oxidizing agent in the presence of BSA produced optically active **2**. The optical purity was strongly dependent on BSA concentration as well as the buffer pH used in the oxidation. For a representative example Fig. 1 shows the effect of BSA concentration on the optical purity of *R*-phenyl isopropyl sulfoxide (**2c**) obtained from the oxidation of the sulfide (**1c**) (5.0 m*M*) with $NaIO_4$ (25.0 m*M*) in a pH 9.2 buffer solution. Above ca. 1.7 m*M* BSA the optical purity of *R*-**2c** showed a constant and highest value of 81%. When decreasing the BSA concentration from this value the optical purity gradually decreased in a saturation change. The reaction mixture was kept clean above ca. 0.6 m*M* of BSA, but below this concentration it began to become turbid. Interestingly, oxidation in such a turbid solution produced **2c** of 69% optical purity at the best. However, further decrease of BSA concentration sharply diminished the optical purity.

On the other hand, Fig. 2 shows the pH effect on the maximum optical purity of **2c**. As is obvious from the figure a dramatic change of optical purity as well as configuration was observed. In the pH range between 9 and 12 the *R* enantiomer was obtained in the highest optical purity of 81%. At pH 8 the *S* enantiomer was produced in excess and the optical purity was very low (19%). The optical purity and configuration were kept unchangable in the pH range between 6 and 8. Below pH 6 the optical purity further decreased, becoming zero at pH 5. The above results of BSA concentration and pH effects demonstrated that the highest stereoselectivity was achieved when BSA was used in ca. $\frac{1}{3}$ molar eq (1.5–1.7 m*M*) to **1c** (5.0 m*M*) at pH > 9.

In addition, the above oxidation revealed the great sensitivity to stereoselectivity as well as reactivity by the kind of oxidizing agent used. Table 1 summarizes the results of chemical yields and optical purities of **2c** in the oxidation with the oxidizing agents other than $NaIO_4$, e.g., H_2O_2, *m*-chloroperbenzoic acid (MCPBA), t-butyl hypochlorite, and t-butyl hydroperoxide in the presence of a

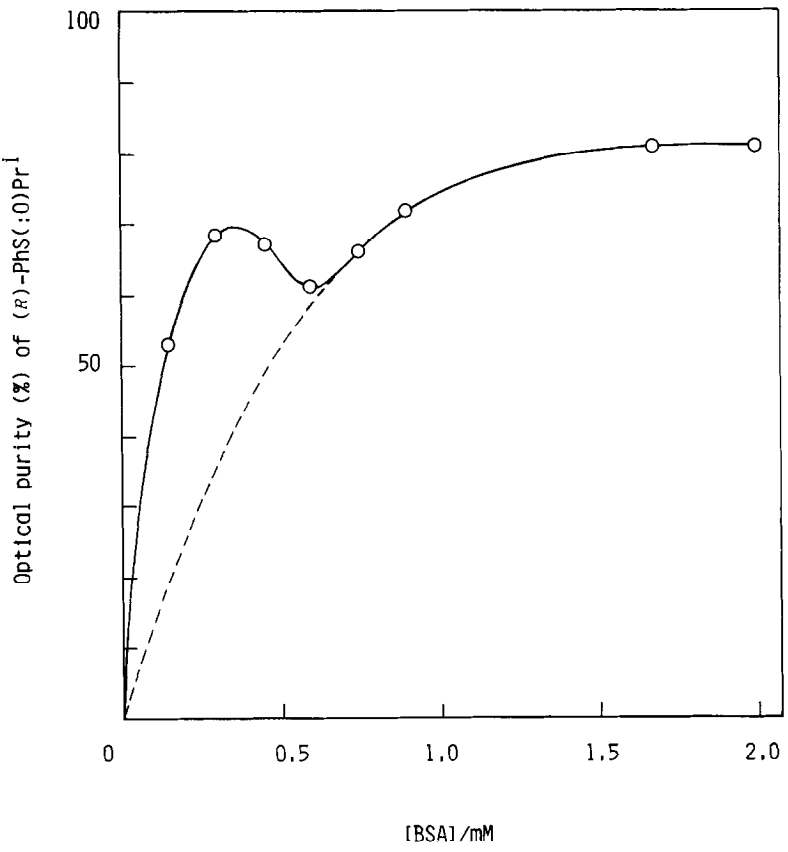


FIG. 1. The effect of BSA (0–2.0 m*M*) on the optical purity of *R*-**2c** in the oxidation of **1c** (5.0 m*M*) with 5 molar eq of $NaIO_4$ at pH 9.2.

metal catalyst of Cu^{2+}, MoO_4^{2-}, or WO_4^{2-}. It is evident from the table that the IO_4^- and H_2O_2 oxidations show higher stereoselectivity and reactivity than the other oxidations. Similarly, the oxidation of *p*-tolyl alkyl sulfides gave sulfoxides of higher optical purity with the use of $NaIO_4$ or H_2O_2, as shown in the case of *p*-tolyl *n*-butyl sulfide (**1l**) (see Table 1). Accordingly, the stereoselective oxidation of the other aromatic sulfides **1** was carried out by using $NaIO_4$ or H_2O_2 under the condition of BSA concentration and buffer pH as above. The chemical yields and optical purities of sulfoxides **2** are given in Table 2. The yield of sulfone was $<5\%$ even when $NaIO_4$, a selective monooxidizing agent (*7*), was used in a large excess. On the other hand, the use of H_2O_2 in a large excess could not avoid overoxidation of sulfoxide to sulfone. However, 5 molar eq of H_2O_2 suppressed sulfone production by $<5\%$ except for the phenyl and *p*-tolyl benzyl sulfide oxidations, in which a considerable amount of sulfone was obtained. Both the phenyl and *p*-tolyl sulfoxides show strikingly improved optical purities, as compared to the previous method using chiral peracids (*8*). Phenyl sulfoxides of fair to high optical purity (30–80%) were obtained by both the $NaIO_4$ and H_2O_2 oxidations, while *p*-tolyl sulfoxides of moderate optical purity (30–50%) were

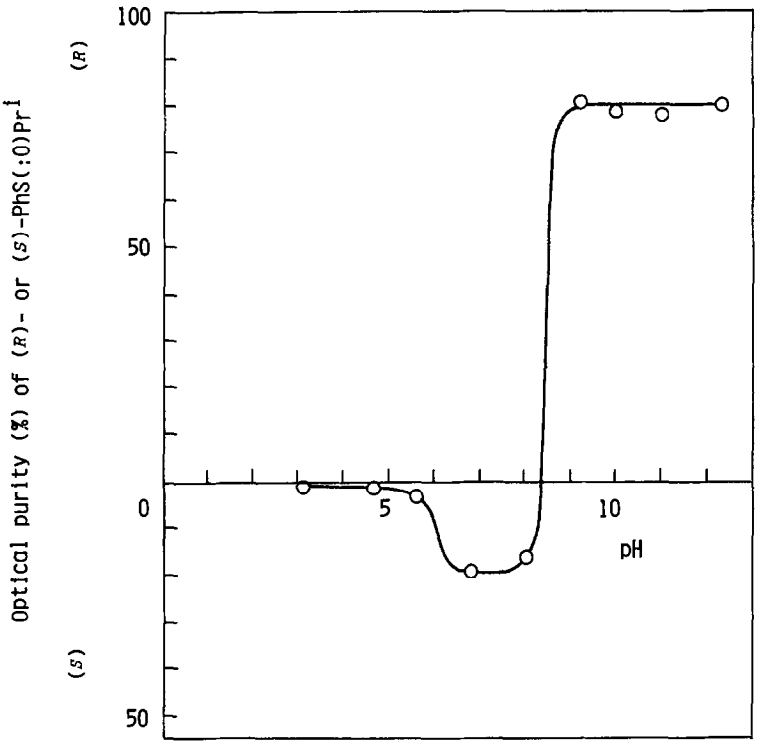


FIG. 2. The pH effect on the maximum optical purity of **2c** obtained by the IO_4^- oxidation of **1c**.

TABLE 1

STEREOSELECTIVE OXIDATION OF PHENYL ISOPROPYL SULFIDE **1c** AND *p*-TOLYL *n*-BUTYL SULFIDE **1l** WITH VARIOUS OXIDIZING AGENTS IN A pH 9.2 BORATE BUFFER SOLUTION CONTAINING BSA AT 25°C

	PhS(:O)Pr^i **2c**			*p*-TolS(:O)Bu^n **2l**		
Oxidizing agent[a]	Chemical yield (%)[b]	Optical purity (%)[c]	Configuration	Chemical yield (%)[b]	Optical purity (%)[c]	Configuration
$NaIO_4$	78	81	*R*	86	52	*S*
H_2O_2	68	78	*R*	79	16	*S*
MCPBA	75	35	*S*	59	8	*S*
Bu^{t}OCl	48	1	*S*	40	2	*S*
Bu^{t}OOH-Cu^{2+d}	27	8	*S*			
Bu^{t}OOH-MoO_4^{2-d}	37	3	*R*			
Bu^{t}OOH-WO_4^{2-d}	54	13	*R*	61	12	*R*

[a] [**1c** or **1l**] = 5.0 m*M*, [oxidizing agent] = 25.0 m*M*, and [BSA] = 1.5–1.7 m*M*. [Cu^{2+}, MoO_4^{2-}, or WO_4^{2-}] = 5.0 m*M* was added in the oxidation with Bu^{t}OOH.

[b] The sulfoxides were isolated purely by preparative silica gel tlc and showed satisfactory spectral data.

[c] Optical purities were calculated from the following literature data for the pure enantiomers: $[\alpha]_D$

TABLE 2

STEREOSELECTIVE OXIDATION OF AROMATIC SULFIDES 1 WITH $NaIO_4$ OR H_2O_2 IN A pH 9.2 BORATE BUFFER SOLUTION CONTAINING BSA AT 25°C

	Aromatic sulfide[a] R^1-S-R^2 1		Aromatic sulfoxide $R^1S(:O)R^2$ 2						
			$NaIO_4$ oxidation			H_2O_2 oxidation			
	R^1	R^2	Chemical yield (%)[b]	Optical purity (%)[c]	Configuration	Chemical yield (%)[b]	Optical purity (%)[c]	Configuration	Reference
(a)	Ph	Me	47	7	*R*				*e*
(b)	Ph	Et	58	29	*R*				*f*
(c)	Ph	Pr^i	78	81	*R*	78	62	*R*	*f*
(d)	Ph	Bu^n	87	36	*R*	82	65	*R*	*f*
(e)	Ph	Bu^i	86	22	*S*	90	65	*R*	*f*
(f)	Ph	Bu^t	86	75	*R*	65	45	*R*	*e*
(g)	Ph	*p*-Tol	29	28	*S*				*g*
(h)	Ph	$PhCH_2$	52	49	*R*	35[d]	71	*R*	*h*
(i)	*p*-Tol	Me	52	6	*R*				*g*
(j)	*p*-Tol	Et	69	35	*S*				*g*
(k)	*p*-Tol	Pr^i	82	34	*S*	73	1	*R*	*g*
(l)	*p*-Tol	Bu^n	86	52	*S*	79	16	*R*	*g*
(m)	*p*-Tol	Bu^t	64	35	*R*	65	12	*R*	*g*
(n)	*p*-Tol	$PhCH_2$	50	40	*R*	31[d]	73	*R*	*g*
(o)	$PhCH_2$	Me	54	2	*S*				*i*
(p)	$PhCH_2$	Et	27	10	*S*				*g*
(q)	$PhCH_2$	Pr^n	67	4	*S*				*f*
(r)	$PhCH_2$	Bu^n	60	1	*S*				*j*
(s)	$PhCH_2$	Bu^t	77	5	*R*				*j*
(t)	$PhCH_2$	*p*-$Bu^tC_6H_4$	43	10	*R*				*h*

[a] [Aromatic sulfide] = 5.0 m*M*, [$NaIO_4$ or H_2O_2] = 25.0 m*M*, and [BSA] = 1.5–1.7 m*M*.

[b] The sulfoxides were isolated pure by preparative silica gel tlc and showed satisfactory spectral data.

[c] Optical purities were calculated from literature data (see last column) for the pure enantiomers.

[d] The considerable amount of sulfones (ca. 30%) was formed in the oxidation of these sulfides. However, the formation yield of sulfones was <5% in the oxidation of the other sulfides.

[e] U. Folli, D. Iarossi, F. Montanari, and G. Torre, *J. Chem. Soc.* (*C*), 1317 (1968).

[f] M. Mikołajczyk and J. Drabowicz, *J. Amer. chem. soc.* **100**, 2510 (1968).

[g] K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, *J. Amer. Chem. Soc.* **87**, 1958 (1965).

[h] B. J. Auret, D. R. Boyd, H. B. Henbest, and S. Ross, *J. Chem. Soc.* (*C*), 2371 (1968).

[i] C. J. M. Stirling, *J. Chem. Soc.*, 5741 (1963).

[j] K. Mislow, M. M. Green, and M. Raban, *J. Amer. Chem. Soc.* **87**, 2761 (1965).

+ 160.2° (acetone) for *R*-**2c** (M. Mikołajczyk and J. Drabowicz, *J. Amer. Chem. Soc.* **100**, 2510 (1978): $[\alpha]_D$ + 187.0° (acetone) for *R*-**2l** (K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, *J. Amer. Chem. Soc.* **87**, 1958 (1965).

[d] Bu^tOOH could scarcely oxidize the sulfides without catalyst.

produced only by the latter oxidation. It should be noted that stereoselectivity drops sharply from the oxidation of alkyl phenyl sulfides to that of the corresponding alkyl *p*-tolyl sulfides. This shows the great sensitivity of this oxidation to changes in substrate structure at positions remote from the sulfur. There is no regular pattern in the configurations of the enantiomeric sulfoxides in the $NaIO_4$ oxidation, while the H_2O_2 oxidation selectively produces the *R* sulfoxides in excess.

The Kinetic Resolution of Racemic **2** *in the Presence of BSA*

When the racemate of **2** was subjected to partial oxidation to the sulfone in the presence of BSA, it was observed that one of the two enantiomers was oxidized faster than the other and the sulfoxide left was optically active. The optical purity increased as the reaction proceeded. For example, Fig. 3 shows the relationship between the recovered yield of remaining unchanged phenyl isobutyl sulfoxide (**2e**) and its optical purity in the oxidation of the racemic **2e** with H_2O_2. In this case the remaining unchanged **2e** showed optical purities of 33 and 69% at 50 and 75% conversions, respectively. The other racemic sulfoxides also exhibited kinetic resolution with a stereoselectivity of 1–21% at ca. 50% completion of oxidation (see Table 3). The observed stereoselectivity is comparable to that obtained by microbial oxidation (usually 0–45%) (*9*) or by chemical methods using chiral agents (5–40%) (*10*). The use of MCPBA in place of H_2O_2 in general revealed less stereoselectivity (4–5%) except for the case of *p*-tolyl isopropyl sulfoxide (**2k**) (24%). As is obvious from the table the stereoselectivity drops sharply from the H_2O_2 oxidation of alkyl phenyl sulfoxides to that of the corresponding alkyl *p*-tolyl

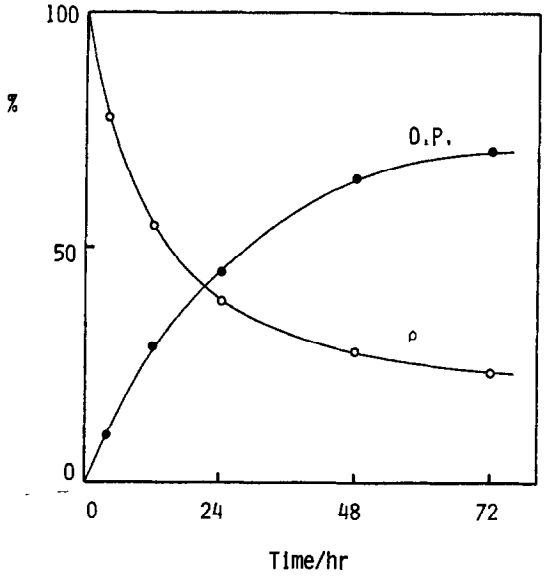


FIG. 3. Kinetic resolution of a racemic **2e** by the oxidation with H_2O_2 in the presence of BSA. (○) *ρ*: The remaining unchanged **2e** (%) starting from the racemic **2e**; (●) O.P.: optical purity (%) of the remaining unchanged *R*-enriched **2e**.

TABLE 3

KINETIC RESOLUTION OF RACEMIC AROMATIC SULFOXIDES 2 WITH H_2O_2 OR MCPBA IN A pH 9.2 BORATE BUFFER SOLUTION CONTAINING BSA AT 25°C

Aromatic sulfoxide $R^1S(:O)R^2$ 2		Enantiomeric sulfoxide 2[a]			
		H_2O_2 oxidation		MCPBA oxidation	
R^1	R^2	Optical purity (%)[b]	Configuration	Optical purity (%)[b]	Configuration
(c) Ph	Pr^i	18	*R*	4	*S*
(d) Ph	Bu^n	16	*R*		
(e) Ph	Bu^i	33	*R*	4	*S*
(f) Ph	Bu^t	5	*R*		
(h) Ph	$PhCH_2$	21	*R*		
(k) *p*-Tol	Pr^i	6	*S*	24	*S*
(l) *p*-Tol	Bu^n	4	*S*	5	*S*
(m) *p*-Tol	Bu^t	1	*S*		
(n) *p*-Tol	$PhCH_2$	17	*R*		

[a] The racemic aromatic sulfoxides were subjected to ca. 50% completion of oxidation, and the unreacted sulfoxides were isolated purely by preparative silica gel.

[b] The optical purities were calculated using the values of optical rotations for the optically pure sulfoxides.

sulfoxides. This again shows the great sensitivity of stereoselectivity to small changes in sulfoxide structure. Interestingly, alkyl phenyl and alkyl *p*-tolyl sulfoxides exhibit different enantioselectivities between the H_2O_2 and MCPBA oxidations. The H_2O_2 oxidation of the former sulfoxides left the *R* enantiomer in excess, while in the case of the latter sulfoxides the remaining unchanged sulfoxides contained the *S* enantiomer in excess. However, such a different enantioselectivity between both the sulfoxides was not observed in the MCPBA oxidation, where the *S*-enantiomeric sulfoxides were obtained in both cases.

The Two-Stage Oxidation of **1** *(Stereoselective Oxidation of* **1** *to the Enantiomeric* **2** *and Its Kinetic Resolution) in the Presence of BSA*

As described in the former section, the use of 5 molar eq of H_2O_2 to **1** selectively gave **2**, and the yield of sulfone was <5%. Increasing formation of sulfone was observed, thereby bringing an increase or decrease in the optical purity of sulfoxide, when the oxidation was carried out by using 10 molar eq of H_2O_2. Fig. 4 shows the time-dependent optical purity change of *R*-**2c** in the oxidation of **1c** (5.0 m*M*) with H_2O_2 (50.0 m*M*) in the presence of BSA (1.5–1.7 m*M*). For the initial period of ca. 12 hr the yield of **2c** increased to 78%, but the optical purity maintained a constant value of 62%. Afterward the optical purity gradually increased while decreasing the yield of **2c** by overoxidizing to the sulfone. When the sulfoxide yield was 47%, the *R*-**2c** showed 93% optical purity. The oxidation of phenyl *n*-butyl sulfide (**1d**) and phenyl isobutyl sulfide (**1e**) with 10 molar eq of

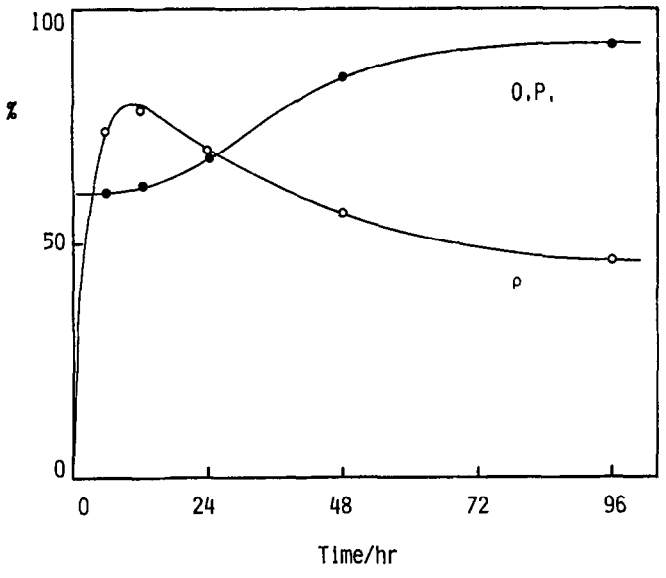


FIG. 4. Time-dependent optical purity change of **2c** obtained by the oxidation of **1c** with H_2O_2 in the presence of BSA. (O) ρ: The produced **2c** (%); (●) O.P.: optical purity (%) of the *R*-enriched **2c**.

H_2O_2 also gave the sulfoxides (**2d**) and **2e** of 90 and 91% optical purities, respectively, in ca. 50% yield. Extremely high optical purities were also achieved by the combined use of $NaIO_4$ for the stereoselective oxidation of sulfide to the sulfoxide and H_2O_2 for the kinetic resolution of the resulting enantiomeric sulfoxide, as shown in the case of **1c** and **1f**. Such an overoxidation does not always bring an increase in the optical purity of sulfoxide, as in a case where kinetic resolution instead decreases the optical purity of sulfoxide. Thus, the H_2O_2 oxidation of *p*-tolyl *n*-butyl sulfide **1l** gave the *R*-enriched **2l** of 17% optical purity in 79% yield. The optical purity decreased to 13% when the sulfoxide yield was 57% by overoxidizing to the sulfone. The other alkyl *p*-tolyl sulfides also showed similar behavior in decreasing the optical purities of sulfoxides by the overoxidation.

DISCUSSION

The stereoselective oxidation of **1** in the presence of BSA gave **2** of maximum optical purity when BSA was used above $\frac{1}{3}$ molar eq at the buffer pH of >9. These reaction conditions are also needed for the production of aromatic alcohols of maximum optical purity in the previous stereoselective reduction of the ketones in the presence of BSA (*1*). Thus, it can be reasonably interpreted that optical activity is induced in **2** by the following effects: (*1*) discrimination between two enantiotopic lone pairs on sulfur atom of **1** bound in the chiral hydrophobic binding domain of BSA, and (*2*) selective attack of an achiral oxidizing agent on one enantiotopic lone pair. It was naturally anticipated that the degree of discrimination between two enantiotopic lone pairs should depend upon the kind of sulfide, and the selectivity in attack of an oxidizing agent on the lone pair should

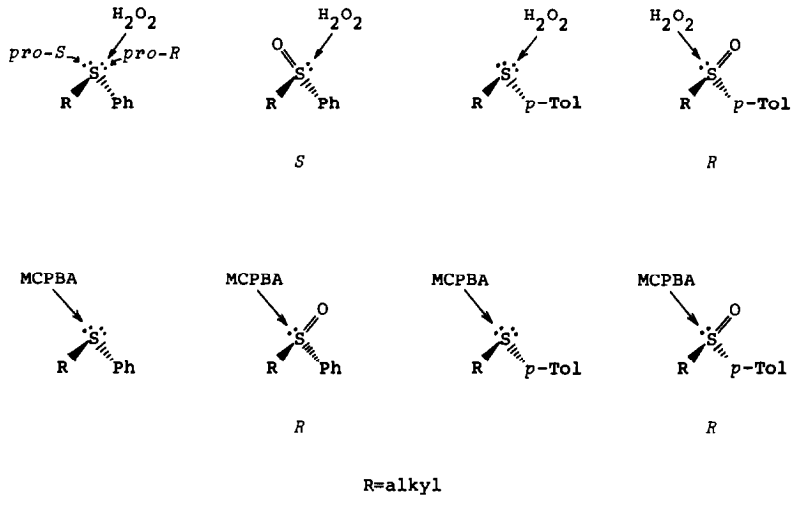
also be dependent on the kind of agent, thereby leading to the production of **2** with strikingly variable optical purity and configuration. Indeed, the present study simply demonstrated the trend that higher stereoselectivities are achieved in the oxidation of alkyl phenyl and *p*-tolyl sulfides rather than alkyl benzyl sulfides, and also by using $NaIO_4$ and H_2O_2 rather than MCPBA, t-butyl hypochlorite and t-butyl hydroperoxide as an oxidizing agent. On the other hand, in regard to configurations it was observed that the $NaIO_4$ oxidation of alkyl phenyl sulfides gave *R*-enriched sulfoxides, while *S*-enriched sulfoxides were obtained from alkyl *p*-tolyl sulfides. The H_2O_2 oxidation of both sulfides produced *R*-enriched sulfoxides.

On the basis of the observation that maximum stereoselectivity is achieved with the use of ca. $\frac{1}{3}$ molar eq of BSA to **1**, it is concluded that one BSA molecule binds three molecules of **1** in the three binding domains, probably in a binding mode of one guest molecule per domain, where asymmetric induction occurs. This is consistent with the recent result of structural analysis by a small-angle scattering X-ray method that shows the presence of three main binding domains in BSA (*11*). The present asymmetric induction occurs only inside the binding domains, while sulfide outside the domains is not stereoselectively oxidized. This is supported by the fact that the optical purity of **2** revealed a saturation change against the BSA concentration in the range of 0.6–2.0 m*M*. At the BSA concentrations of <0.6 m*M* the protein was denatured by a fairly large amount of insoluble sulfide, and the reaction mixture was suspended. Surprisingly, high stereoselectivity (max ca. 70%) was obtained by the oxidation of **1** in the presence of a small amount of the denatured BSA (*12*). It is most likely that the denatured BSA possesses much more binding domains than three in the native BSA as a result of partial destruction of the globular structure. Furthermore, **1** inside the binding domains in the denatured form is still oxidized to **2** with a high degree of stereoselectivity.

Another characteristic of this oxidation is a remarkable change in optical purity and configuration of sulfoxide by the conformational changes of BSA occurring near pH 8–9 and 5–6, which are called as N–B (*13*) and N–F transitions (*14*), respectively. That is, the BSA protein is present as a B-form at pH > 9 as an N-form in the pH range of 6–8, and as an F-form at pH < 5. The respective form provides different chirality to the binding domain, where the observed stereoselectivity will be necessarily different. Of three forms the binding domain in a B-form serves as a most desirable chiral environment for the achievement of the highest stereoselectivity in the sulfide oxidation.

The kinetic resolution of racemic sulfoxide (**2**) left a **2** enantiomer of maximum optical purity by using the same BSA concentration and buffer pH as in the stereoselective oxidation. Accordingly, the above fact suggests that both the enantiomers of **2** are bound in the three main binding domains of BSA and their one enantiomer is oxidized at a faster rate than the other. In addition, the kinetic resolution revealed remarkably different enantioselectivities depending upon the kind of an oxidizing agent used, e.g., H_2O_2 and MCPBA (see Table 3). The partial oxidation of racemic alkyl phenyl and *p*-tolyl sulfoxides with H_2O_2 left the *R* enantiomer in excess for the former sulfoxide and the *S* enantiomer for the latter sulfoxide, while the remaining unchanged sulfoxides by the partial oxidation of

both the sulfoxides with MCPBA contained the *S* enantiomer in excess. When considered in combination with the result of the stereoselective oxidation of alkyl phenyl and *p*-tolyl sulfides with H_2O_2 and MCPBA, the preferential attack of these oxidizing agents on a lone pair on the sulfur atoms of alkyl phenyl and *p*-tolyl sulfides and sulfoxides are summarized in Scheme 2. If it is assumed that both the



sulfides and the corresponding sulfoxides have the same binding mode in the BSA domain, H_2O_2 prefers to attack from the *re*-face direction the lone pair on the sulfur atom except for alkyl *p*-tolyl sulfoxide, while MCPBA always attacks from the *si*-face direction. This obviously shows that the interaction between BSA and an oxidizing agent governs the attacking direction as well as selectivity of the oxidizing agent to an enantiotopically discriminated lone pair on the sulfur atom of sulfide and sulfoxide in the BSA domain, since it is not likely that the binding mode of sulfide and sulfoxide should depend upon the kind of oxidizing agent.

Now that we had obtained some understanding of the stereochemical course ot the oxidation of **1** and **2** in the BSA binding domain, we were next interested in the production of **2** of extremely high optical purity (>90%) (*15*) by the two-stage oxidation of **1**, i.e., the stereoselective oxidation of **1** to the enantiomeric **2** and its following kinetic resolution. The *R*-**2c** of 81% ($NaIO_4$ oxidation) or 62% (H_2O_2 oxidation) optical purity, *R*-**2d** and *R*-**2e** of 65% optical purities (H_2O_2 oxidation), increased their optical purities to >90% by the following kinetic resolution with H_2O_2, when their yields decreased to ca. 50%. In the above kinetic resolution the less favorable *S* enantiomer was oxidized at a faster rate than the favorable *R* enantiomer, thereby leading to the increase of *R*/*S* ratio. Preferential oxidation of the *S* sulfoxides was also observed in the kinetic resolution of their racemic sulfoxides bound beforehand in the BSA domain (see Table 3). The two-stage oxidation of alkyl *p*-tolyl sulfides with H_2O_2 was a remarkable contrast with that of alkyl phenyl sulfides. The optical purities of the initially produced *R*-enriched

sulfoxides was decreased by their kinetic resolution. This shows that the favorable *R* enantiomer is oxidized at a faster rate than the other *S* enantiomer, as is also observed in the kinetic resolution of racemic alkyl *p*-tolyl sulfoxides. The two-stage oxidation of both alkyl phenyl and *p*-tolyl sulfides with MCPBA increased the optical purities of initially produced *S* sulfoxides, as expected from the stereochemical results of each oxidation. On the basis of the above observations it is strongly suggested that the optical purity and configuration of sulfoxides produced by the two-stage oxidation are the cumulative result of stereoselective processes in each stage of sulfide and sulfoxide oxidations. In biological systems certain microorganisms, e.g., *A. niger*, *R. arrhizus*, and *R. stolonifer*, carry out the two-stage oxidation as above and produce sulfoxides of extremely high optical purity (*6*). Since enantiomeric sulfoxides with a different configuration are often formed in the microbial oxidation of sulfides and of the corresponding racemic sulfoxides, an analogous mechanism can be postulated for the two-stage oxidation in the microbial systems.

EXPERIMENTAL

Optical rotations were measured with a Perkin–Elmer Model 241 polarimeter using a quartz cell with a 100-mm path length at 25°C. Separation by tlc was carried out on a silica gel 60 F_{254} tlc plate (20 × 20-cm layer, thickness 0.25 mm) obtained from Merck Ltd.

Materials. Distilled water was from Daiwa Chemical Ltd., and solvents for optical rotation measurement were spectroscopic grade from Nakarai Chemical Ltd. BSA was Fraction V grade from Armour Ltd., and used without further purification. Aromatic sulfides used were prepared according to the method by Ipatieff *et al.* (*16*) and purified by fractional distillation. The corresponding sulfoxides were prepared by the oxidation of the sulfides with 1.1 molar eq of $NaIO_4$ in water or acetone–water at 0°C, and purified by CCG separation on silica gel. A 30% H_2O_2 solution was from Mitsubishi Chemical Ltd., and the other oxidizing agents of $NaIO_4$, MCPBA, t-butyl hypochlorite, and t-butyl hydroperoxide and metal catalysts of $CuSO_4$, Na_2MoO_4, and Na_2WO_4 were from Nakarai Chemical Ltd.

The stereoselective oxidation of **1** *in the presence of BSA.* An appropriate **1** (0.25 mmol) was added to 50 ml of a buffer solution containing BSA. After gentle stirring of the mixture at 25°C for 2 h an oxidizing agent [$NaIO_4$, H_2O_2, MCPBA, t-butyl hypochlorite or t-butyl hydroperoxide with $CuSO_4$, Na_2MoO_4, or Na_2WO_4 (0.25 mmol)] (1.25 mmol) was added and the reaction was continued by stirring for a further 2 hr at 25°C. Sodium hydrogensulfite (1.25 mmol) was added to the reaction mixture, followed by extraction with three 100-ml portions of ether, drying over magnesium sulfate, and concentrating to give the oily or solid residue. The pure **2** was separated from the unreacted **1** and the sulfone on tlc using ether as an eluant. To the measured amount of this isolated **2** was added 2 ml of the solvent used in the literature, and the optical rotation was measured at 25°C. The optical purity was calculated from $[\alpha]_D$(obs.)/$[\alpha]_D$(max) × 100 (%), using the

known optical rotation of the optically pure sulfoxide in the same solvent. The above oxidation was carried out under the condition of different pHs in the range of 3–12 and different BSA amounts in the range of 0–0.1 mmol. After workup as above the optical purity of **2** was obtained in each case.

The kinetic resolution of racemic **2** *in the presence of BSA.* A racemate of **2** (1.25 mmol) was added to 250 ml of a buffer solution (pH 9.2) containing BSA (0.415–0.5 mmol). After gentle stirring of the mixture at 25°C for 2 hr, a 30% H_2O_2 solution or MCPBA (12.5 mmol) was added and the reaction was continued by stirring at 25°C. At each reaction period of 6, 12, 24, 48, and 72 hr sodium hydrogensulfite (1.25 mmol) was added to 50 ml of the reaction mixture, followed by extraction with three 100-ml portions of ether, drying over magnesium sulfate, and concentrating to give the residue of the unreacted **2** and the sulfone. The pure **2** was separated from the sulfone on tlc, and the recovered yield and optical purity were obtained. From the relationship between optical purity of **2** and its recovered yield the optical purity of the unreacted **2** at ca. 50% completion of oxidation was determined.

The two-stage oxidation of **1** *in the presence of BSA.* An appropriate **1** (1.25 mmol) was added to 250 ml of a buffer solution (pH 9.2) containing BSA (0.415–0.5 mmol). After gentle stirring of the mixture at 25°C for 2 hr, $NaIO_4$ (6.25 mmol), a 30% H_2O_2 solution (12.5 mmol), or only the H_2O_2 solution (12.5 mmol) was added and the reaction was continued by stirring at 25°C. At each reaction period of 6, 12, 24, 48, and 96 hr 50 ml of the reaction mixture was taken out and the produced **2** was isolated according to the workup as above. The isolated yield and optical purity of **2** were obtained at each reaction period.

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