

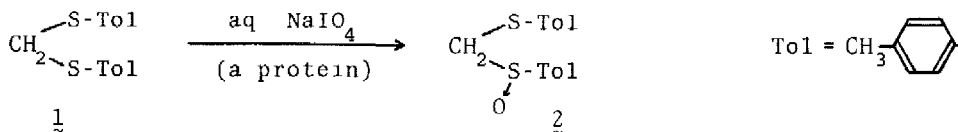
A TWO-PHASE REACTION CATALYZED BY A PROTEIN — ASYMMETRIC OXIDATION
OF FORMALDEHYDE DITHIOACETALS WITH AQUEOUS SODIUM METAPERIODATE

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Abstract. We examined whether a protein could catalyze two-phase oxidation of formaldehyde dithioacetals with aqueous sodium metaperiodate and bovine serum albumin was found to be effective and give the corresponding S-oxides in optically active forms.

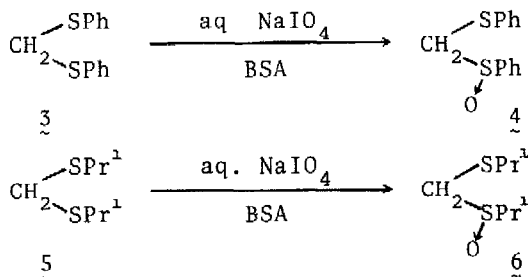
For two-phase reactions, there have been developed various catalysts, such as quaternary ammonium (or phosphonium) salts and crown ethers, which usually contain both hydrophobic and hydrophilic sites and can accelerate the reaction by bringing one of the reactants into the phase of the other reactant ¹⁾ However, the water-soluble proteins with hydrophobic cavities have received scant attention as phase transfer reagents in the literature. They can take a certain substance in the organic phase into the aqueous phase for reaction when added to a two-phase aqueous-organic system. If the product formed in the hydrophobic cavity is replaced with the organic phase substance, these proteins will behave as phase transfer catalysts and their ability to orient bound molecules is expected to provide a mean of developing asymmetric syntheses



As a diagnostic reaction for this conception, we chose oxidation of formaldehyde di-*p*-tolyl dithioacetal (1) with aqueous sodium metaperiodate in the presence of a protein because asymmetric synthesis using its optically active S-oxide derivative (2), which was less hydrophobic than 1, was one of our subjects and alkyl aryl sulfides bound to a carrier protein, bovine serum albumin (BSA), was oxidized by sodium metaperiodate to afford the corresponding sulfoxide in an optically active form ²⁾ When 1 and sodium metaperiodate (one

equiv to $\underline{1}$) were added to a borate buffer solution (pH 9.2, about 50 ml per one mmol of $\underline{1}$), $\underline{1}$ remained insoluble to form an organic phase. After stirring this mixture at 30 °C for 3 days, no reaction took place and $\underline{1}$ was recovered unchanged. Addition of a commercially available protein, either bovine serum β -globulin (fraction III)³⁾ (0.005 mol-equiv) or egg albumin³⁾ (0.02 mol-equiv) to this system brought about oxidation of $\underline{1}$, although slightly, and the S-oxide derivative ($\underline{2}$) was produced in about 5% yield over 18 h. Interestingly, large enhancement of the oxidation rate was observed in the presence of 0.02 mol-equiv of BSA³⁾. Thus, after stirring for 18 h, we obtained $\underline{2}$ in a 37% yield together with the unchanged $\underline{1}$ (56%) and the S,S'-dioxide (5%) of $\underline{1}$. It should be noted that the thus-obtained $\underline{2}$ was optically active and the optical purity was calculated to be 41%⁴⁾.

Furthermore, how the amount and the concentration of BSA influence the optical purity of $\underline{2}$ was also examined. To an aqueous solution (the borate buffer of pH 9.2) of BSA were added $\underline{1}$ and sodium metaperiodate, and the resulting mixture was stirred at 30 °C. Then, the reaction mixture was extracted with diethyl ether and benzene-diethyl ether, dried over anhydrous sodium sulfate, evaporated *in vacuo*, and subjected to column chromatography on silica gel to give $\underline{2}$. The results were summarized in Table and it was shown that the optical purity of $\underline{2}$ increased with increasing amount of BSA and reached to the uppermost limit when the molar ratio of BSA : $\underline{1}$ was about 0.1. However, even in the presence of a catalytic amount of BSA (the molar ratio of BSA : $\underline{1}$ = 0.02), a higher optical purity (58%) was attained by reducing the volume of the buffer solution, *i.e.* increasing the concentration of BSA. The similar phenomena were observed in oxidation of formaldehyde diphenyl dithioacetal ($\underline{3}$) and formaldehyde diisopropyl dithioacetal ($\underline{5}$), both of which afforded the corresponding S-oxides ($\underline{4}$ ⁹⁾ and $\underline{6}$) in higher optical purities with higher concentration of BSA when the same amount of BSA was used (see Table).



These facts suggest that, in the present system, the factor controlling the optical purity of formaldehyde dithioacetal S-oxide ($\underline{2}$, $\underline{4}$, or $\underline{6}$) is not the relative amount of BSA to $\underline{1}$, but the concentration of BSA, in sharp contrast with the conclusion given in oxidation of alkyl aryl sulfides bound to BSA with

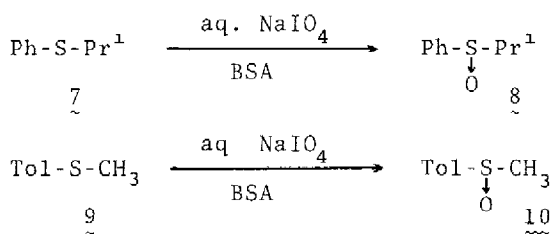
Table Oxidation of Sulfides with Aqueous Sodium Metaperiodate in the Presence of Bovine Serum Albumin (BSA)^a

| Sulfide | BSA (mol-equiv) ^b | NaIO ₄ (mol-equiv) ^b | Concn of BSA ^c (mM) | Reaction Time (h) | Product | | |
|----------------|------------------------------|--|--------------------------------|-------------------|-----------------------|---------|------------------|
| | | | | | Yield(%) ^d | O P (%) | |
| 1 | 0.005 | 1.0 | 0.1 | 100 | S-2 | 30 [9] | 38 |
| 1 | 0.01 | 1.0 | 0.2 | 24 | S-2 | 31 [5] | 37 |
| 1 | 0.02 | 1.0 | 0.4 | 24 | S-2 | 37 [5] | 41 |
| 1 | 0.02 | 0.8 | 2.0 | 22 | S-2 | 29 [6] | 58 |
| 1 | 0.03 | 1.0 | 0.6 | 24 | S-2 | 37 [5] | 44 |
| 1 | 0.05 | 1.2 | 1.0 | 18 | S-2 | 32 [4] | 50 |
| 1 | 0.1 | 1.5 | 2.0 | 24 | S-2 | 30 [3] | 60 |
| 1 | 0.2 | 1.9 | 4.0 | 18 | S-2 | 28 [4] | 53 |
| 1 ^e | 0.33 | 2.0 | 2.0 | 5 | S-2 | 44 [6] | 20 |
| 3 | 0.02 | 1.0 | 0.4 | 18 | S-4 | 49 [4] | 30 ^{g)} |
| 3 | 0.02 | 1.0 | 2.0 | 22 | S-4 | 45 [8] | 36 ^{g)} |
| 5 | 0.02 | 1.0 | 0.4 | 21 | 6 | 59 [0] | -- ^f |
| 5 | 0.02 | 1.0 | 2.0 | 20 | 6 | 23 [0] | -- ^g |
| 7 | 0.02 | 1.0 | 0.4 | 18 | R-8 | 76 | 60 |
| 7 | 0.02 | 1.1 | 2.0 | 24 | R-8 | 72 | 20 |
| 9 | 0.02 | 1.0 | 0.4 | 18 | R-10 | 80 | 16 |
| 9 | 0.02 | 1.0 | 2.0 | 24 | R-10 | 77 | 1.6 |

^a stirred at 30 °C. ^b mol-equiv to the sulfide ^c a borate buffer solution of pH 9.2

^d The value in the bracket indicates the yield of the formaldehyde dithioacetal S,S'-dioxide

^e according to the procedure described in ref. 2 ^f [α]_D²⁰ -6.91° ^g [α]_D²⁰ -9.64°



sodium metaperiodate 1/3 mol-equiv of BSA was required for producing the maximum optical purity.²⁾ Hence, oxidation of isopropyl phenyl sulfide (7) and methyl *p*-tolyl sulfide (9) was carried out in the presence of 0.02 mol-equiv of BSA. Under the 2.0 mM concentration of BSA, the corresponding sulfoxides 8 and 10 were formed in lower optical purities (20% and 1.6%, respectively). When the concentration of BSA was diminished to 0.4 mM, the optical purities of 8 and 10 increased remarkably to 60% and 16%, respectively,¹⁰⁾ with high chemical

yields as shown in Table

In conclusion, two-phase oxidation of various sulfides with aqueous sodium metaperiodate can be catalyzed by BSA, a carrier protein,¹¹⁾ although the preferable concentration of BSA depends upon the type of sulfide.

We are continuing our studies to provide some insights into the detailed mechanism and to extend the present reaction system to other types of reactions.

Acknowledgment: The authors wish to express our gratitudes to Dr. Toyonari Sugimoto of Kyoto University for kindly sending helpful comments and the preprint of his paper (ref 2) before its publication We thank the Asahi Glass Foundation for Industrial Technology for financial support of this work

References and Notes

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- 3) The molecular weights of bovine serum β -globulin, egg albumin, and bovine serum albumin (BSA) were assumed to be 90,000, 66,000, and 66,000, respectively. These proteins were purchased from Tokyo Kasei Kogyo Company, Wako Pure Chemical Industries, and Sigma Chemical Company, respectively.
- 4) The $[\alpha]_D$ of optically pure 2, 8, and 10 were taken as 76° ,⁵⁾ 169° ,⁶⁾ and 145.5° ,⁷⁾ respectively.
- 5) L. Colombo, C. Gennari, and E. Narisano, *Tetrahedron Lett*, 1978, 3861 For the $[\alpha]_D$ of S-2, 76° ⁸⁾ was also given
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- 9) This compound (4) was oxidized with sodium metaperiodate in methanol-water to give the S,S'-dioxide derivative as a mixture of the *meso*- and *dl*-isomers. The ratio of these isomers was determined by an NMR analysis (90 MHz) and the optical purity of the *dl*-isomer, which was equal to that of 4, was calculated by using lit⁸⁾ $[\alpha]_D$ 358°
- 10) At the present time, we cannot explain concisely the inverse effect of the BSA concentration in comparison with that observed in oxidation of 1, 3, and 5.
- 11) We cannot eliminate the possibility that, under the present conditions, BSA undergoes any structural change caused by the presence of a large amount of the sulfide and/or oxidation with sodium metaperiodate.

(Received in Japan 2 March 1980)