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Asymmetric Microbial Oxidation of Formaldehyde Dithioacetals[1)]

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Incubation of formaldehyde dithioacetals with growing cells of *Corynebacterium equi* IFO 3730 afforded a variety of oxidation products depending on the structure of the substrates. The products with sulfoxide moiety were optically pure and had *R* configuration.

A dithioacetal group serves not only as a protecting group of carbonyl compounds, but also as a "masked acyl anion", because two mercapto groups stabilize the central methylenic anion.[2)] Thus, it will be potentially interesting to introduce an asymmetric center to a dithioacetal group because the resulting compound will serve as a chiral acyl anion equivalent. It has been already demonstrated by Ogura *et al.* that the chirality on sulfur atom of dithioacetals can be transferred to a carbon atom.[3)]

Microbial transformations have been demonstrated to be often effective for the introduction of chirality to prochiral compounds. Hitherto, only a few examples of enzymatic oxidation of dithioacetals have been demonstrated, and the optical purities of the products were not enough for the synthetic application.[4)]

Studies on microbial transformation in our laboratory have shown that *Corynebacterium equi* IFO 3730 has an enzyme system which catalyzes the oxidation of various sulfides to optically active sulfoxides and sulfones.[5)] Now, we wish to report the results of application of this system to oxidation of thioacetals.

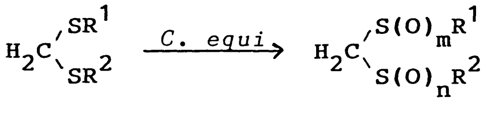
In a 500-ml Sakaguchi flask, were added 90 ml of the sterilized inorganic medium,[6)] 2 ml of hexadecane, and 0.1 to 0.4 ml of a dithioacetal **1**. The mixture was inoculated with 10 ml of a suspension of grown cells of *C. equi*, and incubated for 3 to 7 days at 30 °C on a reciprocatory shaker. The broth was extracted with a 100 ml portion of ethyl acetate three times, and the combined extracts were concentrated under reduced pressure. Separation of the remaining hexadecane by column chromatography on silica gel gave a mixture of the substrate and the oxidized products amounting to almost quantitative recovery of sulfur-containing compounds. The oxidation products were isolated and purified by preparative TLC on silica gel and identified by comparing their ^{1}H-NMR, IR, and mass spectra with those of authentic specimens.[7)] The major products are summarized in Table 1.

A variety of products were obtained depending on the structure of substrates. The substrates which have alkyl chain with large numbers of carbons tend to be oxidized smoothly (compd b, d). The similar tendency has been observed in the oxidation of terminal olefins,[8)] secondary alcohols,[9)] and alkyl aryl sulfides[5)] by *C. equi*. Diphenyl dithioacetal was most resistant to oxidation and afforded the mono sulfone in a low yield (compd a). In oxidation of unsymmetric alkyl aryl dithioacetals, the sulfur atom linked to the alkyl chain was oxidized in all cases (compd d, e, f).

Oxidation of dibutyl dithioacetal and methyl phenyl dithioacetal resulted in the formation of products which have sulfoxide moiety (2c, 2f).[10] Both sulfoxides were confirmed to be optically pure by ^{1}H-NMR in the presence of chiral shift reagent (Fig. 1).

The absolute configuration of sulfoxides is determined by Pirkle's method[11] and CD spectra.[12] Sulfoxides are known to form 1:1 solvates with (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)-ethanol 3 (TFAE) (Fig. 2). The shielding effect of the

Table 1. Oxidation of Formaldehyde Dithioacetals



$$H_2C<^{SR^1}_{SR^2} \xrightarrow{C.\ equi} H_2C<^{S(O)_mR^1}_{S(O)_nR^2}$$

1 2

Compd	Substrate	Concn /%[a)]	Cult./day	Product	Yield/%	e.e./%	Δε of CD(nm)
a	$H_2C<^{SPh}_{SPh}$	0.1	7	$H_2C<^{SO_2Ph}_{SPh}$	34[b)]	-	-
b	$H_2C<^{SC_8H_{17}}_{SC_8H_{17}}$	0.2	3	$H_2C<^{SO_2C_8H_{17}}_{SO_2C_8H_{17}}$	100	-	-
c	$H_2C<^{SC_4H_9}_{SC_4H_9}$	0.1	7	$H_2C<^{SO_2C_4H_9}_{SOC_4H_9}$	70	>95	-2.2(223)[d)] -1.9(229)[e)]
d	$H_2C<^{SPh}_{SC_8H_{17}}$	0.2	3	$H_2C<^{SPh}_{SO_2C_8H_{17}}$	76	-	-
e	$H_2C<^{SPh}_{SC_4H_9}$	0.1	7	$H_2C<^{SPh}_{SO_2C_4H_9}$	44[c)]	-	-
f	$H_2C<^{SPh}_{SCH_3}$	0.1	7	$H_2C<^{SPh}_{SOCH_3}$	47[b)]	>95	-1.1(218)[d)] -1.4(231)[e)]

a) ml substrate / 100 ml medium

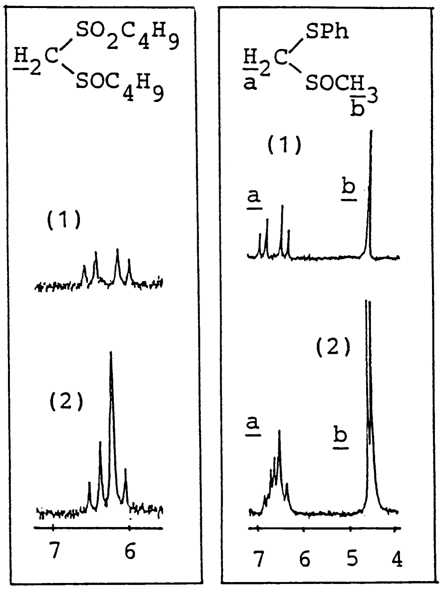
b) The remaining part is recovered starting material.

c) A small amount of $PhSCH_2SOC_4H_9$ (12%) was identified in addition to starting material.

d) Measured in EtOH.

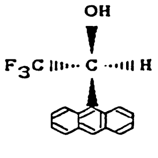
e) Measured in c-C_6H_{12}.

anthryl group allows us to expect that the methylene proton resonances occur at higher field for the (Sc,Ss)-solvates (Fig. 2-A, 2-C) than the (Sc,Rs)-solvates (Fig. 2-B, 2-D). The ^{1}H-NMR signal due to the methylene group of racemic 2c split into three peaks (doublet and singlet), corresponding to two enantiomers by adding 2 mol equivalents of a chiral solvent TFAE 3. Under the same conditions 2c obtained from microbial oxidation showed a methylene signal of doublet in the lower field due to one enantiomer.$^{13)}$ These results show that the methylene group of the product 2c is trans to the anthryl group (Fig. 2-B), which led to the conclusion that 2c has R configuration. In a similar manner, while the signal due to methylene of racemic 2f split into two sets of quartet, the one of the product 2f appeared as only one set of quartet in lower field.$^{13)}$ Hence, the product 2f is determined to have R configuration.



(A) (B)

Fig. 1. Eu(hfc)$_3$-shifted ^{1}H-NMR Spectra of 2 . (A) 2c; (B) 2f (1) microbial oxidation product; (2) racemic



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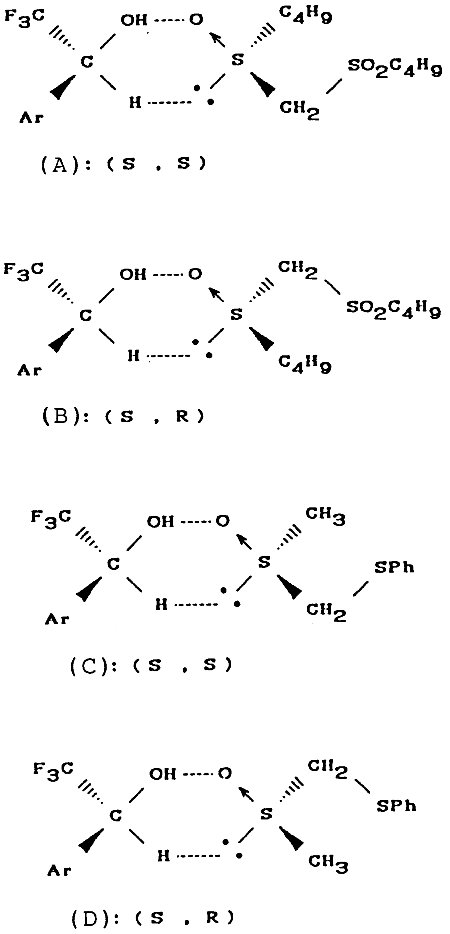

Fig. 2. Configuration of solvates of 2 with TFAE 3.

Mislow et al. have shown that a relation exists between the absolute configuration of alkyl methyl and alkyl aryl sulfoxides and the ORD Cotton effect. The sulfoxides which show a negative Cotton effect, centered at the absorption band of S-O group, have been demonstrated to have R configuration. We studied the Cotton effect with CD spectra. Compared with ORD spectra, CD spectra are independent of other absorptions, and give the simple and important informations for the study of stereochemistry. The results were summarized in Table 1. In both cases of the products 2c and 2f, the CD spectra showed negative values, which indicates that both sulfoxides have R configuration. This result agreed with the one obtained by Pirkle's method.

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6) The medium consists of $(NH_4)_2HPO_4$ 10 g, KH_2PO_4 2 g, $MgSO_4\cdot7H_2O$ 0.3 g, $FeSO_4\cdot7H_2O$ 10 mg, $ZnSO_4\cdot7H_2O$ 8 mg, $MnSO_4\cdot4H_2O$ 8 mg, yeast extract 0.2 g, and H_2O to make 1000 ml (pH 7.2).

7) Authentic samples were prepared as follows: $(C_8H_{17}SO_2)_2CH_2$, $C_4H_9SO_2CH_2SOC_4H_9$, and $PhSCH_2SOCH_3$, by oxidation of dithioacetals with H_2O_2 in acetic acid; $PhSCH_2SO_2Ph$, $PhSCH_2SO_2C_8H_{17}$, and $PhSCH_2SO_2C_4H_9$, by the coupling of phenylthiomethylmagnesium chloride with alkanesulfonyl chloride; K. Ogura, M. Fujita, K. Takahashi, and H. Iida, Chem. Lett., 1982, 1697.

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10) $C_4H_9SO_2CH_2SOC_4H_9$ 2c: IR (NaCl) 2915, 2848, 1450, 1315, 1295, 1025 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (6H, t, J=7.5 Hz, 2 x CH_3), 1.64 (4H, m, 2 x $C\underline{H}_2CH_3$), 3.00 (2H, t, J=7.2 Hz, $SOC\underline{H}_2CH_2$), 3.26 (2H, t, J=7.2 Hz, $SO_2C\underline{H}_2CH_2$), 4.17 (2H, s, CH_2); MS m/z (rel. intensity) 241 (37, M+1), 223 (10), 184 (40), 127 (44), 103 (63), 63 (100), 57 (45). $PhSCH_2SOCH_3$ 2f: IR (NaCl) 3050, 2960, 2900, 1575, 1475, 1435, 1040, 740, 690 cm^{-1}; NMR ($CDCl_3$) δ 2.57 (3H, s, CH_3), 3.78 (1H, d, J=12 Hz, CH_2), 4.02 (1H, d, J=12 Hz, CH_2), 7.33 (5H, m, Ph); MS m/z (rel. intensity) 186 (1, M^+), 123 (100), 109 (5), 77 (13), 45 (34).

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13) Chemical shift of CH_2 flanked to two sulfur atoms: 2c; $\underline{3.9509}$, $\underline{3.9511}$, 3.9401. 2f; $\underline{4.0415}$, $\underline{4.0073}$, 3.9975, 3.9633, $\underline{3.8314}$, $\underline{3.7985}$, 3.8021, 3.7679. All peaks were observed for racemic compounds, while underlined peaks were strongly observed for enzymatic oxidation products.

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