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OXYGENATION OF ALKYL SULFIDES WITH FERROUS PERCHLORATE/ ASCORBIC ACID/OXYGEN SYSTEM

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Summary: In the oxidation of alkyl sulfides bearing acidic α-hydrogens either with phenobarbital induced rabbit liver microsomal cytochrome P-450, or with the Udenfriend's model system (ferrous perchlorate/ascorbic acid/oxygen system), both S-dealkylation and S-monooxygenation took place concurrently. Meanwhile, in the oxidation of simple alkyl sulfides, stereoselective S-monooxygenation was found to occur predominantly.

Although there are several examples of N-dealkylation of alkyl amines and O-dealkylation of alkyl ethers such as N-methylanilines, methylamphetamine, p-nitroanisole, etc., with cytochrome P-450 oxygenase[1] (eq. 1), the enzymatic oxidative dealkylation of alkyl sulfides was tried only with methylthio compounds by molecular oxygen using a non-purified enzyme system containing NADPH.[2]

$$R\text{-}X\text{-}CH_3 \xrightarrow[NADPH/O_2]{P\text{-}450} [\ R\text{-}X\text{-}CH_2OH\ ] \longrightarrow R\text{-}XH + HCHO \qquad (1)$$

R = aryl, alkyl X = NR, NH, O

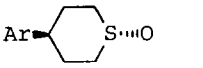
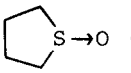
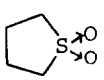
However, neither the formation of sulfoxide was checked, nor the whole pattern of oxidation was compared with that of chemical oxidations with a few typical oxidizing agents. We now have carried out the oxidation of alkyl sulfides both with phenobarbital induced rabbit liver microsomal cytochrome P-450, and with the Udenfriend's model system which contains both ferrous perchlorate and ascorbic acid,[3] and found that both S-dealkylation and S-monooxygenation took place concurrently.

When the β-keto sulfide (4) was incubated with a rabbit liver microsome [cytochrome P-450$_{LM}$ (1 x 10^{-4} mmole) in 48 mg protein],[4] the disulfide (11), the S-dealkylated product, and the S-oxygenated product, i.e., sulfoxide (12), were found to be formed in 17% and 7% yields, respectively. Treatment of 4-p-chlorophenylthiane (1) with the microsome, however, gave only the S-oxygenated products (7) and (8). Meanwhile, when α-substituted sulfides having acidic α-hydrogens, such as the β-keto sulfide (4) and cyanomethyl phenyl sulfide (5), were treated with the Udenfriend's system,[5] the corresponding sulfoxides and the disulfides were similarly obtained. The amount of disulfide formed from (4) was higher than that form (5).[6] Further, when cyanomethyl phenyl sulfide (5) was oxidized with the Udenfriend's system in media of three different pH values, the S-dealkylation was found to increase with the increase of the pH value [relative yield of (11); pH 4.5 (1), pH 9.45 (1.8), pH 11.5 (2.4)].

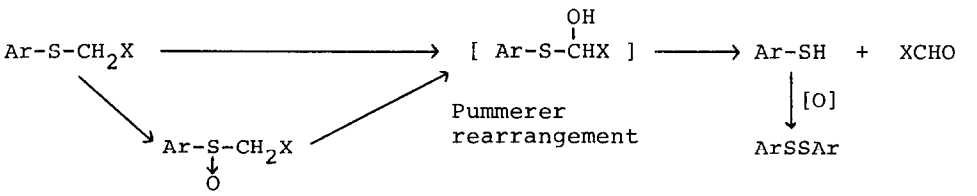
Upon oxidation with the Udenfriend's system, simple alkyl sulfides such as the thiane (1), thiolane (2) and thioanisole (3) gave only the corresponding sulfoxides. The reactivity of the sulfides appears to depend qualitatively on the electron density of the respective sulfur atom; namely the relative rates of oxidation fall in the following order (1) ≃ (2) > (3) ≃ (4) ≃ (5) > (9), suggesting that the S-oxygenation takes place by the electrophilic attack of the oxidant on the sulfur atom. This is in keeping with the <u>trans</u> selectivity in the oxidation of the thiane (1) with electrophilic chemical oxidants such as peroxides and peracids.[7,8]

These observations clearly indicate that the S-dealkylation takes place with alkyl sulfides bearing an α-acidic methylene group in both enzymatic and chemical oxidations. Meanwhile, there are two conceivable mechanisms for the formation of the disulfide; one is the Pummerer rearrangement of the sulfoxide,[9] and the other is the direct α-hydroxylation of the sulfides. The α-hydroxysulfides thus formed are very readily hydrolyzed to form the corresponding thiols which undergo further oxidation to afford the disulfides (eq. 2). When the sulfoxide (13) was treated with the Udenfriend's oxidizing system, the sulfoxide was recovered nearly quantitatively (>95%) and a very small amount of the arenesulfonic acid (ca. 1%) was obtained, however, there was no formation of the disulfide.

Table Oxidation of Sulfur Compounds
system A : rabbit liver microsome
system B : Fe(II)/ascorbic acid/O_2

substrate[a]	oxidation system	ascorbic acid[b]	time (hr)	product[c] (isolated yield)
 (1) Ar = p-ClC_6H_4	A		22	 trans (7) cis (8) (6.3%, (7)/(8) = 67/33)
(1)	B	2	33	(7) + (8) (32%, (7)/(8) = 70/30)
 (2)	B	1.5	22	 (9) (20%)
$PhSCH_3$ (3)	B	9.5[d]	36	$Ph-\overset{\overset{O}{\downarrow}}{S}-CH_3$ (10) (17%)
$PhSCH_2COPh$ (4)	A		22	PhSSPh (11) (17%) + $Ph-\overset{\overset{O}{\downarrow}}{S}-CH_2COPh$ (12) (7%)
(4)	B	3	25	(11) (12%) + (12) (4%)
$PhSCH_2CN$ (5)	B	1.6	22	(11) (7%) + $Ph-\overset{\overset{O}{\downarrow}}{S}-CH_2CN$ (13) (6%)
 (9)	B[e]	6.4	44	 (14) (31%)
PhSH (6)	B	1	6	(11) (100%)

a) generally, 1.5 - 2 equivalent amounts of the substrates were used to ferrous perchlorate.
b) this column indicates equivalent amounts of ascorbic acid used to ferrous ion.
c) yields of isolated products were calculated based on the amount of ferrous perchlorate used, and the unreacted substrates were recovered.
d) a large amount of ascorbic acid was used for less reactivity of this substrate
e) a large excess of the sulfoxide was used.



(2)

Thus the S-dealkylation is considered to proceed through the incipient formation of the α-hydroxysulfide like in the case of the N-dealkylation, and not through the incipient formation of the corresponding sulfoxide.

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References and Notes

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2. A.H. Conney, Pharmacol. Rev., 19, 317 (1967). b) J.F. Henderson and P. Mazel, Biochem. Pharmacol., 13, 1471 (1964).
3. This oxidation system (ref. 10) is considered to involve the "activated oxygen species" as the oxidant. see G.A. Hamilton, in "Molecular Mechanisms of Oxygen Activation", ed. by O. Hayaishi, Ch. 10, Academic Press, New York (1974).
4. The oxidation of alkyl sulfides (10 mg) was carried out with rabbit liver microsome (48 mg protein) at 36°C in phosphate buffer (pH 7.25) containing NADPH (10 μmole) as the essential cofactor.
5. In a typical experiment, 30 ml of acetate buffer (pH 4.5) was added to a 30 ml of acetone solution of sulfide (1.4 - 2 mmole) containing ferrous perchlorate (1 mmole) and ascorbic acid (1 - 3 mmole). Sulfides, sulfoxides and disulfides thus obtained were separated through silica-gel chromatography column with chloroform as the solvent, while sulfinic and sulfonic acids in aqueous layer were analyzed by liquid chromatography.
6. see also, T. Numata, Y. Watanabe and S. Oae, Tetrahedron Lett., 4933 (1978).
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8. The electrophilic attack on the trans side is theoretically favored, since in the highest occupied molecular orbital of the thiane (1) the coefficient of the trans side of the sulfur is much larger than that of the cis side. (J. Klein, private communication)
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