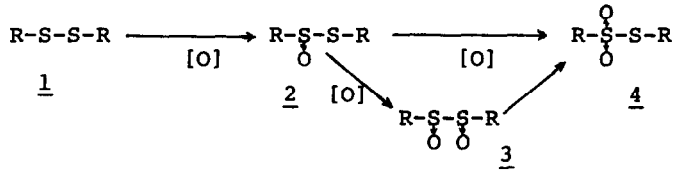
Tetrahedron Letters No. 13, pp 1195 - 1198, 1977. Pergamon Press. Printed in Great Britain.

THE OXIDATION OF UNSYMMETRICAL THIOLSUFINATE : EVIDENCE FOR α-DISULFOXIDE AS AN INTERMEDIATE

S. Oae, Y.H. Kim, T. Takata and D. Fukushima
Department of Chemistry, University of Tsukuba, Niiharigun,
Ibaraki, 300-31 Japan

(Received in Japan 14 February 1977; received in UK for publication 21 February 1977)

Although the formation of α-disulfoxide as an intermediate in the oxidation of a disulfide to the corresponding thiolsulfonate or further oxidation products has been suggested both in vivo[1] and vitro[2] reactions for a long time, no evidence or isolation of α-disulfoxide(3) has hitherto been reported yet. The initial step of oxidation of a disulfide is undoubtedly the formation of the corresponding thiolsulfinate(2), which can be readily obtained under any mild oxidation condition. As to the subsequent step to form the thiolsulfonate(4), there are two conceivable pathways, i.e., one involving the direct further oxidation of sulfinyl sulfur to the thiolsulfonate and the other involving the initial oxidation of sulfenyl sulfur to form " α-disulfoxide"(3) which in the subsequent step transfers oxygen to form the thiolsulfonate(4) as shown below.



The latter possibility seems more plausible in view of the more nucleophilic nature of the sulfenyl sulfur than the sulfinyl sulfur and indeed the formation of " α-disulfoxide" as an intermediate has been suggested both in vivo and in vitro-oxidation of cysteine to its thiolsulfonate, without any experimental evidence.

During the course of our study on the oxidation of unsymmetrical disulfides, we have found that oxidation of ^{18}O-labeled methyl benzenethiolsulfinate(5)

with an equimolar amount of peracetic acid gave, along with others, i.e., 8 and 9, phenyl methanethiolsulfonate(7) containing ^{18}O atom(70% of ^{18}O label of 5), which appears to be derived from the hitherto-imaginary "α-disulfoxide"(6). Thus we wish to report the results which appear to support the incipient formation of the intermediary α-disulfoxide in the oxidation of both the disulfide and the thiolsulfinate to the corresponding thiolsulfonate and sulfonic acid.

$$\underset{\underset{5}{}}{Ph\text{-}\overset{\overset{18}{O}}{S}\text{-}S\text{-}CH_3} \xrightarrow{\text{eq. } AcO_2H} \underset{7}{Ph\text{-}S\text{-}S^{18}O_2CH_3} + \underset{8}{Ph\text{-}S\text{-}S^{18}O_2Ph} + \underset{9}{CH_3\text{-}S\text{-}S^{18}O_2CH_3} \qquad (1)$$

^{18}O-Labeled methyl benzenethiolsulfinate(5) was prepared by treating methanethiol with ^{18}O-labeled benzenesulfinyl chloride which was prepared by treating diphenyl disulfide with Cl_2 gas in ^{18}O-labeled acetic anhydride[3], and then carefully purified by repeated column chromatography at a low temperature[4] (silica gel, 2.2x30 cm, 0°, solvent system; n-hexane:chloroform:ethylacetate= 4:1:1). The oxidation of ^{18}O-labeled 5 with an equimolar amount of peracetic acid at 20° for 6 h gave phenyl methanethiolsulfonate,7(25%), phenyl benzenethiolsulfonate,8(25%), methyl methanethiolsulfonate,9(13%) and the starting material,5(19%), but no detectable amount of the disproportionation products,as shown in eq. (1). The pure products 7,8, and 9 were separated by repeated column chromatography[5] and then subjected to the ^{18}O-analysis. Results of ^{18}O tracer and other experiments are summarized in Table I.

The initial step of oxidation undoubtedly involves the electrophilic attack of peracetic acid on the sulfenyl sulfur atom of 5 to form phenyl methyl α-disulfoxide(6) which is then considered to be converted rapidly to the three respective thiolsulfonates(7, 8, and 9). The most plausible mechanism to explain the oxidation may be the following.

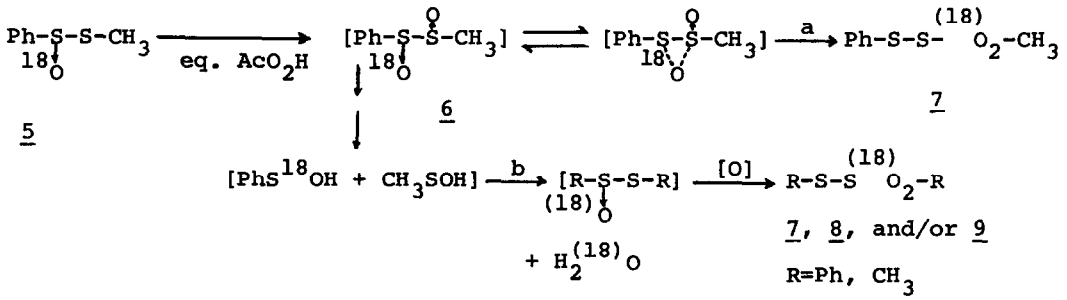


Table I Oxidation of ^{18}O Labeled Unsymmetrical Thiolsulfinate with Peracetic acid

Substrate (Exc. ^{18}O atom%)	Mol. ratio AcO_2H/Sub	Reactn. temp. (°C)	Reactn. time (h)	Products	Exc. ^{18}O atom%	Incorporated ^{18}O% a)
$PhS(^{18}O)-SCH_3$ (0.515)	1	20	6	$PhSS^{18}O_2CH_3$	0.178	70
				$PhSS^{18}O_2Ph$	0.319	129
				$CH_3SS^{18}O_2CH_3$	0.170	67
$PhS(^{18}O)-SCH_3$ (0.53)	1	20	0.5	$PhS(^{18}O)-SCH_3$ b)	0.52	99
"	1	20	2.5	"	0.50	95
$PhS(O)-SCH_3$	0 c)	20	20	$PhS(O)-SCH_3$ d)		

a) The content of ^{18}O incorporation of 5 was calculated based on the number of oxygen atom and ^{18}O atom analyzed. b) In oder to examine possible ^{18}O exchange between substrate, 5 and peracetic acid, the oxidation was stopped after 0.5 and 2.5 h, respectively. The compound, 5 which was carefully recovered revealed only 1-5% of ^{18}O exchange within experimental error. c) The control experiment for checking the stability of the starting material, 5 was done under the same condition without peracetic acid in aqueous acetic acid and aqueous sulfuric acid in acetonitrile, respectively (pH=1.7). d) Starting material, 5 was quantitatively recovered without any disproportionation or decomposition.

The α-disulfoxide (6) could not be detected during the oxidation at ca. 35° by nmr spectrum. Kice et al.[6] also reported that aromatic α-disulfoxide was not stable enough to be detected at -20° by nmr technique. The product (7) must be derived rapidly from 6 as shown by pathway a or b. If a is the only path, 7 should contain 100% of ^{18}O-label of 5, but 7 retained only 70% of ^{18}O. Therefore, some other route, for instance, path b derived from 6 must be taken into consideration. Cleavage of sulfur-sulfur bond of unsymmetrical α-disulfoxide 6 may form both phenyl- and methyl-sulfenic acid. Meanwhile, the sulfenic acids are known to be readily converted to the corresponding thiolsulfinates[7]. These thiolsulfinates formed by pathway b can be readily oxidized further to the corresponding thiolsulfonates (7, 8, and 9) in this oxidation system. Thus, the mechanism of the formation of 5 is not very simple, however the ^{18}O tracer experiment suggests strongly that the oxidation involves

"α-disulfoxide" as an intermediate at least to the extent of 70%. Other possible mechanisms, such as intramolecular ^{18}O migration to the adjacent sulfur atom before oxidation of 5 to the thiolsulfonate and the disproportionation of 5 to the thiolsulfonate and disulfide are also possible. However these two mechanisms can be ruled out, since the control experiment of 5 under the condition with the same acidity(aqueous sulfuric acid in acetonitrile and aqueous acetic acid, pH=1.7, respectively) at 20° for 20 h gave no detectable amount of any product except the starting material(5).

References and Foot-notes

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2). a) For a review, see; W.E. Savige and J.A. Maclared, in Organic Sulfur Compound, ed. by N. Kharasch, Vol. 2, Chapt. 15, Pergamon Press, Oxford, 1966. b) T.F. Lavine, J. Biol. Chem., 113,583(1936). c) G. Toennies and T.F. Lavine, J. Biol. Chem., 571(1936); T.F. Lavine, G. Toennies and E.C. Wagner, J. Am. Chem. Soc., 56, 242(1934). d) G.E. Utzinger, Experimentia, 17, 374 (1961).

3). a) S. Oae and K. Ikura, Bull. Chem. Soc. Japan, 39, 1306(1966). b). S. Oae, K. Ikura and Y. Shimano, J. Synthetic Org. Chem. Japan, 28, 50(1970).

4). Impure 5 was unstable at ca. 25° : disproportionation to disulfide and thiolsulfonate occurred.

5). Column chromatographies were 3 times repeated by using different solvent system(n-hexane:chloroform:ethylacetate=4:1:1, n-hexane:acetone=10:1, and then finally, n-hexane:chloroform:ethylacetate=4:1:1).

6). M. Chau and J.L. Kice, Org. Division(18) in Abstract, 172nd ACS National Meeting, San Francisco, 1976. After this work was completed, Kice's paper appeared in J. Am. Chem. Soc., 98, 7711(1976).

7). The formation of both aromatic and alkyl thiolsulfinates in an attempt to prepare these sulfenic acids was already reported [a), b), c)].

$$2[RSOH] \longrightarrow RS(=O)SR + H_2O$$

a) N. Kharasch, W. King and T.C. Bluce, J. Am. Chem. Soc., 77, 931(1955).

b) F. Ostermayer and D.S. Tarbell, J. Am. Chem. Soc., 82, 3752(1960).

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