Halogen–Hydrogen Halide Catalysis of the Oxidation of Thiols to Disulfides by Sulfoxides

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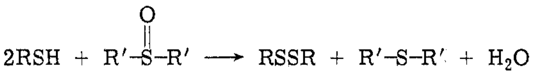
Received June 14, 1974

Halogens and hydrogen halides (not including fluorine and hydrogen fluoride) have been found to be exceptional catalysts for the oxidation of aliphatic and araliphatic thiols to disulfides by sulfoxides. They are significantly more effective catalysts than ordinary (nonhydrohalic) acids. A given halogen and its hydrogen halide provide an equivalent catalytic effect. Water has a retarding effect. A mechanism in which the halogen and hydrogen halide are coupled is suggested. Catalytic ability is in the order Br > I > Cl. HCl in combination with a minor amount of iodine is a particularly effective catalyst. In the analogous oxidation of aromatic thiols, these catalysts are not distinctive from ordinary acids, and the oxidation is not retarded by water. This is interpreted as the aforementioned mechanism having diminished applicability for the oxidation of aromatic thiols. Iodine–HI catalysis provides a vivid indicator for completion of oxidation. With bromine–HBr catalysis, this is less so.

Wallace and Mahon[1] have reported acid catalysis of the oxidation of aliphatic and araliphatic thiols to disulfides by sulfoxides (1). The catalysis was observed at 100° and found to be mild. No hydrogen halide (hydrohalic acid) was included in the study.

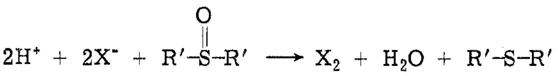
On the other hand, I observed ready oxidation at significantly lower temperatures in the presence of hydrogen halides (HX) or halogens. When iodine or HI is used as the catalyst, there is a pronounced color change from colorless to amber when the thiol is exhausted. A similar but much less intense color change can be observed with bromine or HBr.

These observations suggested the operation of reactions 2[2] and 3.[3] Reaction 2 may provide the acid for catalysis when halogen is used. On the other hand, a coupling of reactions 2 and 3 could provide an alternative form of catalysis.



$$2RSH + R'-\overset{\overset{\displaystyle O}{\|}}{S}-R' \longrightarrow RSSR + R'-S-R' + H_2O \quad (1)$$

$$2RSH + X_2 \longrightarrow RSSR + 2H^+ + 2X^- \quad (2)$$



$$2H^+ + 2X^- + R'-\overset{\overset{\displaystyle O}{\|}}{S}-R' \longrightarrow X_2 + H_2O + R'-S-R' \quad (3)$$

For the study of halogen and HX catalysis, the determination of completion time based on color appearance seemed convenient but only proved practical with iodine species. To provide a basis for comparison of catalytic ability of all halogens and acids in general, a test based upon reaction 2 using iodine in dimethyl sulfoxide (DMSO) was devised. Though not as satisfactory as the in situ appearance of iodine color, lack of decolorization in this test established when 98–99% of the thiol had reacted. Also, because of the generally diminished solubility of disulfides in sulfoxides and higher melting points as compared with thiols, there were other indications of reaction extent.

Solutions of a thiol in excess sulfoxide containing minor amounts of halogen or acid were heated until completion was indicated by the in situ appearance of amber (iodine) color, if applicable, or by the no-decolorization test or for an otherwise meaningful length of time. With solutions of 2-methyl-2-propanethiol (MPT) in DMSO heated at 65°, the catalytic effect of iodine and concentrated hydriodic acid was readily apparent in the inverse effect of concentration on completion time (Table I). Bromine and concentrated hydrobromic acid had the same effect but were more efficient.

Table I[a]
Oxidation of 2-Methyl-2-propanethiol by Dimethyl Sulfoxide

Catalyst	Catalyst concn	Completion time, hr
I_2	0.68	8.2
I_2	1.36	2.0
I_2	1.36	1.9[b]
I_2	1.36	1.7[c]
I_2	2.48	0.3
HI	1.37	3.5
HI	2.74	0.9
Br_2	0.48	4.8
Br_2	0.72	1.7
Br_2	1.44	0.2
HBr	0.91	1.8
HBr	1.40	0.8
HCl	1.42	Inc_7
HCl	2.84	8.0
HCl	1.42	4.5[d]
HF	1.42	NAR_7[d]
CH_3SO_3H	1.39	NAR_7[d]
HNO_3	1.42	NAR_7[d]

[a] Thiol/sulfoxide molar ratio, 0.41; temperature, 65°. Catalyst concentration and water concentration (Table II) are expressed in moles/100 mol of sulfoxide. Where the catalyst is a halogen, its concentration is expressed as HX equivalents. Inc_n indicates an apparent reaction as evidenced by separation (crystallization) of product disulfide but otherwise incomplete in *n* hours. NAR_n indicates no apparent reaction in *n* hours. [b] Oxidation conducted under a nitrogen atmosphere. [c] Completion time determined by the no-decolorization test. [d] Thiol/sulfoxide ratio is half of that indicated for the table.

The discrepancy in the catalytic effect of equivalent amounts of the halogen and its HX is due to the retarding effect of water introduced through the use of an aqueous HX, for adding water to the halogen in amount equal to that present with the HX gave equal completion times (Table II). Increased water caused still more retardation.

With concentrated hydrochloric acid as the catalyst, completion did not occur readily except with a high HCl concentration (Table I). Alternatively, ready completion was attained with a moderate HCl concentration when the amount of thiol was reduced. With hydrofluoric, methanesulfonic, or nitric acid, there was no apparent reaction even with a low MPT concentration, apparent reaction being indicated by the appearance of a new, bis(*tert*-butyl) disulfide phase.[4]

Completion time on admixture of halogen species and of nonhydrohalic acids with halogen or HX was also investigated (Table III). HCl with a minor amount of iodine was a

Table II[a]
Effect of Water on Oxidation of 2-Methyl-2-propanethiol by Dimethyl Sulfoxide

Catalyst (concn)	Water concn	Completion time, hr
I_2 (1.36)	Nil	2.0
I_2 (1.36)	7.4	3.5
57% HI (1.37)	7.4	3.5
Br_2 (1.44)	Nil	0.2
Br_2 (1.44)	6.8	0.8
48% HBr (1.40)	6.7	0.8
29% HBr (1.40)	15.5	2.0

[a] Thiol/sulfoxide molar ratio, 0.41; temperature 65°.

Table III[a]
Mixed Catalysis, Oxidation of 2-Methyl-2-propanethiol by Dimethyl Sulfoxide

Principal catalyst (concn)	Enhancer catalyst (concn)	Completion time, hr
HCl (1.42)	None	Inc$_7$
HCl (0.95)	I_2 (0.067)	0.8
HBr (0.91)	None	1.8
HBr (0.91)	I_2 (0.063)	1.5
H_2SO_4 (1.13)	I_2 (0.062)	NAR$_3$
CH_3SO_3H (1.40)	I_2 (0.065)	NAR$_5$
HF (1.42)	I_2 (0.070)	NAR$_7$[b]
I_2 (0.68)	None	8.2
I_2 (0.62)	CH_3SO_3H (0.73)	6.8
I_2 (1.24)	None	2.3
I_2 (1.24)	CH_3SO_3H (1.40)	1.0
I_2 (2.48)	None	0.3
HCl (1.42)	None	4.5[b]
HCl (1.42)	CH_3SO_3H (1.40)	3.0[b]

[a] Thiol/sulfoxide molar ratio, 0.41; temperature, 65°. [b] See footnote *d*, Table I.

Table IV
Oxidation of 2-Methyl-2-propanethiol by Other Sulfoxides

Catalyst	Catalyst concn	Temp, °C	Completion time, hr
By TMSO (Thiol/Sulfoxide Molar Ratio, 0.47)			
I_2	1.55	50	0.4
I_2	1.55	25	9.5
HI	1.55	50	0.8
Br_2	1.60	25	0.1[a]
HBr	1.60	50	0.1[a]
HBr	1.60	25	0.3
HCl	3.22	50	7.0
CH_3SO_3H	3.18	50	NAR$_{14}$
By DPSO (Thiol/Sulfoxide Molar Ratio, 0.49)			
I_2	1.62	50	1.5
HBr	1.66	50	0.8
HCl	3.36	65	8.8
CH_3SO_3H	3.31	65	NAR$_{20}$

[a] Noticeably exothermic.

Table V
Oxidation of Thiols by Dimethyl Sulfoxide

Catalyst	Catalyst concn	Temp, °C	Completion time, hr
Dodecanethiol (Thiol/Sulfoxide Molar Ratio, 0.40)			
I_2	1.24	60	8.8
HBr	1.40	60	2.2
HCl	1.42	75	4.5[a]
CH_3SO_3H	1.39	75	NAR$_{10}$[a]
HCl + I_2	0.95, 0.067[b]	60	1.2
CH_3SO_3H + I_2	1.39, 1.24[b]	60	3.5
α-Toluenethiol (Thiol/Sulfoxide Molar Ratio, 0.40)			
I_2	1.36	60	1.6
HBr	1.40	60	0.9
HCl	1.42	60	1.7[a]
CH_3SO_3H	1.39	60	NAR$_9$[a]

[a] See footnote *d*, Table I. [b] Respectively.

markedly more effective catalyst than HCl alone. The analogous addition of iodine to HBr gave only a minor enhancement. Similar trace addition of iodine to sulfuric, methanesulfonic, and hydrofluoric acids did not produce effective catalysts. The addition of 1 equiv of a strong acid, methanesulfonic acid, to iodine or HCl produced an enhancement, though the effect was less than that of another 1 equiv of the halogen species.

Catalysis of the oxidation of MPT by sulfoxides was also checked using tetramethylene sulfoxide (TMSO) and dipropyl sulfoxide (DPSO) (Table IV). Results completely paralleled those obtained with DMSO, including a slightly longer completion time relative to halogen where an aqueous HX was used. With TMSO oxidation could be conducted at 25°.

The oxidation of dodecanethiol by DMSO was similarly investigated (Table V). Again, oxidation of the thiol went to completion within a number of hours at 60–75° when a minor amount of halogen or HX was present. With methanesulfonic acid present, completion was not attained in 10 hr at 75° even with half the usual thiol concentration, nor was apparent reaction indicated by crystallization of didodecyl disulfide on cooling. As in the oxidation of MPT, an admixture of HCl and a minor amount of iodine had a marked catalytic effect. Use of methanesulfonic acid along with iodine showed an increase in catalytic effect over that of iodine alone.

Results for the oxidation of α-toluenethiol by DMSO at 60° are given in Table V. Again, halogen species were effective catalysts; methanesulfonic acid was not.

There is a definite distinction between halogen–HX catalysis (not including fluorine–HF catalysis) and ordinary (nonhydrohalic) acid catalysis in that the former occurs readily at moderately elevated temperatures at which the latter is not particularly apparent. This along with equivalent catalytic effect of a halogen and its HX, retardation by water, and acceleration by ordinary acid, supports the probability that halogen–HX catalysis is a consequence of the coupling of reactions 2 and 3. It would seem that halogen is in the HX or other colorless form initially. Acceleration by nonhydrohalic acid may be through a common ion effect in reaction 3. Increase in the reverse of reaction 3[3,5] may account for retardation by water, which would indicate progressive retardation since water is a product.

The pronounced catalysis by HCl in the presence of a minor amount of iodine may be due to the formation of a mixed halogen.

The situation is entirely different in the oxidation of aromatic thiols, which, even without catalyst, may be oxidized by sulfoxides at room temperature[6] though Whiting[7] has reported acid catalysis. Halogen, HX, and methanesulfonic acid were all found to be effective catalysts for the DMSO oxidation of benzene- and 2-naphthalenethiol (Table VI). There was no great variation in completion time and no readily apparent trend. Addition of water to the HBr-catalyzed reaction did not slow the oxidation. Thus, it would

Table VI
Oxidation of Aromatic Thiols by Dimethyl Sulfoxide

Catalyst	Catalyst concn	Completion time, hr
Benezenethiol (Thiol/Sulfoxide Molar Ratio, 0.46; Temperature 25°)[a]		
I_2	1.36	4.0[b]
I_2	1.36	8.0
HBr	1.40	2.9
HBr	1.40	2.7[c]
HCl	1.42	3.5
CH_3SO_3H	1.39	4.2
none		Inc$_{21}$
2-Naphthalenethiol (Thiol/Sulfoxide Molar Ratio, 0.25; Temperature, 25°)[a]		
HBr	1.40	2.0
HBr	1.40	1.5[c]
HCl	1.42	1.5
CH_3SO_3H	1.39	2.5
none		25.

[a] Noticeably exothermic. [b] See footnote *c*, Table I. [c] Additional water added so that its total initial concentration was 15.5 mol/100 mol of DMSO.

seem that here a true or proper acid catalysis[8] competes favorably with the sequence represented by reactions 2 and 3. These may do little more than respectively provide the acid when a halogen is used and signal completion.

With each MPT–sulfoxide combination, a preparative experiment was undertaken. Through isolation and determination of properties, it was ascertained that bis(*tert*-butyl) disulfide and a reduced sulfoxide (a sulfide) were products in reasonable amount consistent with the expected stoichiometry. The disulfide was obtained in 80–87% of the theoretical yield; the sulfide, 76–84%. For dodecane-, α-toluene-, benzene-, and 2-naphthalenethiol, completed oxidations were checked for the disulfide product and its yield by work-up and isolation. In each case, the anticipated disulfide was obtained in about 90% of the theoretical yield.

Halogen–HX catalysis significantly enhances the ease with which aliphatic and araliphatic thiols may be oxidized to disulfides by sulfoxides and can be expected to be synthetically useful. Yields are excellent and possibly quantitative except for crystallization and mechanical losses. The catalysis seems to be applicable for oxidation of a wide variety of aliphatic thiols. Indeed, the tertiary thiol MPT, which otherwise oxidizes with difficulty,[9] served as a useful model for much of this study.

Experimental Section

Reagents. The DMSO, halogens, hydrohalic acids, nitric acid, and sulfuric acid were reagent grade. TMSO and DPSO were dried over molecular sieves and distilled. The concentration of the acids was as follows unless otherwise indicated: HI, 57%; HBr, 48%; HCl, 37%; HF, 48%; HNO_3, 70%; and H_2SO_4, 96%. The methanesulfonic acid was redistilled; hence, essentially 100%. Commercial thiols were used directly unless of practical grade, in which case they were redistilled.

General Procedure for Determination of Completion Time. Experiments were run with 0.10–0.13 mol of sulfoxide and a thiol/sulfoxide molar ratio of less than 0.50. A mixture of the thiol, sulfoxide, catalyst, and any added water was heated under reflux within 1° of the temperature indicated while stirring magnetically.

Completion times were determined as follows. When no iodine-containing catalyst was used, a drop (0.03 ml) of the reacting mixture was periodically withdrawn and added to 1 ml of a 0.025% solution of iodine in DMSO until decolorization no longer occurred (limit of thiol detection in this test, about 0.026 *M*). When an iodine-containing catalyst was used, reaction was continued until the in situ appearance of iodine color unless otherwise indicated. (Completion occurs later on the basis of in situ color appearance when the no-decolorization test is applied). When two phases were present, the no-decolorization test was applied to both phases except when the second phase was a crystalline solid. Results are given in Tables I–VI.

Bis(*tert*-butyl) Disulfide (Preparative Example). A solution of 18 ml (0.157 mol) of MPT and 0.66 g of iodine (0.0052 mol as HI) in 30 ml of TMSO was cautiously heated[10] under reflux at 50° until a deep amber color appeared (about 0.5 hr). After cooling, the mixture was shaken with 50 ml of water containing sufficient sodium carbonate to remove the amber color. The organic phase was extracted twice with 25 ml of water. Combined aqueous extracts were then extracted thrice with 20-ml portions of ether. Combined organic phases were dried over anhydrous potassium carbonate and distilled. Obtained was 5.8 g of tetramethylene sulfide (84% of theory). The boiling point and melting point of the mercuric chloride derivative were in agreement with reported values.[11] Further distillation at a pressure of 22 mm gave 11.4 g of bis(*tert*-butyl) disulfide (82% of theory). The melting point and boiling point agreed with reported values.[12]

Recovery of Disulfide from Completion Experiments (Dodecane-, α-Toluene-, Benzene- and 2-Naphthalenethiol). Following completion, dimethyl sulfide was removed by subjecting the reaction mixture to vacuum. Twenty milliliters of water was stirred in to completely precipitate the disulfide, which was then collected and recrystallized from an appropriate solvent. Identity was confirmed by melting point.

Registry No.—I_2, 7553-56-2; HI, 10034-85-2; Br_2, 7726-95-6; HBr, 10035-10-6; HCl, 7647-01-0; CH_3SO_3H, 75-75-2; MPT, 75-66-1; DMSO, 67-68-5; TMSO, 1600-44-8; DPSO, 4253-91-2; dodecanethiol, 112-55-0; α-toluenethiol, 110-53-8; benzenethiol, 108-98-5; 2-naphthalenethiol, 91-60-1; bis(*tert*-butyl) disulfide, 1518-72-5.

References and Notes

(1) T. J. Wallace and J. J. Mahon, *J. Org. Chem.*, **30**, 1502 (1965).

(2) A well-known procedure for the oxidation of thiols to disulfides. (a) E. E. Reid, "Organic Chemistry of Bivalent Sulfur", Vol. 1, Chemical Publishing Co., New York, N.Y., 1958, p 118; Vol. 3, 1960, p 363; (b) A. Schöberl and A. Wagner in Houben-Weyl, "Methoden der Organischen Chemie", Vol. 9, 4th ed, Georg Thieme Verlag, Stuttgart, 1955, pp 59–65.

(3) (a) R. H. Rynbrandt, *Tetrahedron Lett.*, 3553 (1971); (b) W. O. Ranky and D. C. Nelson in "Organic Sulfur Compounds", N. Kharasch, Ed., Pergamon Press, Elmsford, N.Y., 1961, p 173. Halogens form adducts with sulfides, but for simplicity this is not shown.

(4) Through appropriate admixture of DMSO, bis(*tert*-butyl) disulfide, water, dimethyl sulfide, and catalyst, it was determined that "no apparent reaction" is less than 60% of theoretical completion for the methanesulfonic acid catalyzed experiment.

(5) D. Landini et al., *Tetrahedron Lett.*, 2691 (1964).

(6) T. J. Wallace, *J. Am. Chem. Soc.*, **86**, 2018 (1964).

(7) L. V. Whiting, Ph.D. Thesis, McGill University, 1970.

(8) The mechanism of such acid catalysis has been discussed. See ref 1 and 7.

(9) T. J. Wallace and H. A. Weiss, *Chem. Ind.* (*London*), 1558 (1966).

(10) Should this or similar preparations be undertaken on a larger scale, ample cooling capacity would be well advised. Alternatively, the gradual addition of thiol to the sulfoxide–catalyst mixture might be considered.

(11) (a) Reference 2a, Vol. 3, p 90; (b) Heilbron, "Dictionary of Organic Compounds", Vol. 5, 4th ed, Oxford University Press, London, 1965, p 2999.

(12) Reference 2a, Vol. 3, p 396.