The Oxidation of Organic Divalent Sulfur by Iodine. II. The Equilibrating Thiol–Iodine–Disulfide–Hydrogen Iodide System in Acetic Acid and Evidence for Sulfenyl Iodide Intermediates[1]

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Spectrophotometric observations of solutions consisting initially of thiol and iodine in acetic acid, or of disulfide and hydrogen iodide in acetic acid, give evidence that this is an equilibrating system which probably involves three reactions (eq 3–5). Practical difficulties prevented the determination of the value for the equilibrium constant for the overall system, but the equilibrium constant for reaction 5 in AcOH has been found to be 1.1 (±0.1) × 10^6. Studies on the titration of 3-mercaptopropionic acid with iodine in acetic acid containing increasing amounts of water or anhydrous sodium acetate show that displacement of the equilibrium toward the disulfide side depends on the equilibrating reaction between hydrogen iodide and base.

In its simple, stoichiometric form the reaction for the oxidation of thiols to disulfides by iodine in aqueous so-

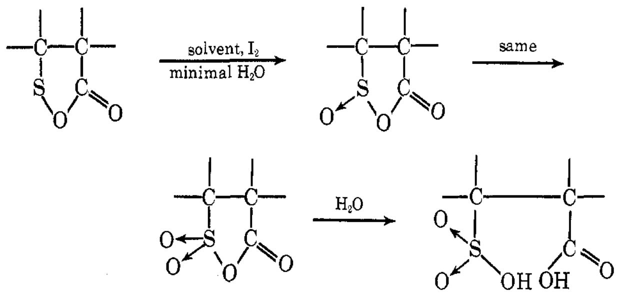
$$2\text{RSH} + \text{I}_2 \xrightarrow[\text{I}^-]{\text{H}_2\text{O}} \text{RSSR} + 2\text{HI} \qquad (1)$$

lution has been known for decades. The first comprehensive suggestion concerning the mechanism by which this reaction might take place came, not from studies on simple models, but from a study of the iodination of proteins. Fraenkel-Conrat,[4] employing conditions under which the iodination of tyrosyl residues would be rather slow, observed that tobacco mosaic virus rapidly consumed 2 equiv of iodine for each sulfhydryl group. He attributed this behavior to the formation of sulfenyl iodide groups and successfully tested the assumption by adding cysteine to his modified protein, whereupon the bound iodine was lost and unsymmetrical disulfide was formed. "The observed formation

$$\text{RSH} + \text{I}_2 \longrightarrow \text{RSI} + \text{HI} \xrightarrow{\text{R'SH}} \text{RSSR}' + \text{HI}$$

of sulfenyl iodide groups under the influence of iodine suggests a more general hypothesis for the mechanism of oxidation of SH groups, even in cases in which the disulfide group is the only reaction product. Thus, a formulation based on assumption of two consecutive bimolecular reactions, rather than one termolecular reaction, appears now preferable...."[4] More recent work has only served to corroborate his views. Cunningham and Nuenke[5] followed spectrophotometrically the uptake of iodine by a number of proteins and found that the stoichiometry was particularly clean-cut in the case of β-lactoglobulin and that the sulfenyl iodide was remarkably stable in neutral aqueous solution.[6] Much earlier studies[7] demonstrated the relative stability of 2-methyl-2-propanesulfenyl iodide and, quite recently, further studies on the relative stability and spectral characteristics of this compound have been reported.[8]

From a study of the iodometric titration of a variety of thiols as a function of the initial concentration of thiol, we[9] demonstrated that all thiols have at least some tendency to consume more than the stoichiometric amount of iodine as the initial concentration of thiol is decreased and that thiols with a carboxyl group attached to a carbon atom β to the sulfur atom are particularly susceptible to overoxidation. As a possible accounting for the first generalization, we suggested that attack of the sulfenyl iodide by the much less nucleophilic water is gradually favored as the much more nucleophilic thiolate ions become scarcer and that the sulfenic acid thus formed would be further oxidized by iodine. To account for the second generalization we proposed a preferential intramolecular attack by the carboxylate anion on the sulfenyl sulfur to displace an iodide ion and form a five-membered cyclic intermediate[9b] which would then undergo oxidation by iodine after hydrolysis. Consideration of the possibility that further oxidation might precede terminal hydrolysis suggested that it might be possible to isolate the proposed cyclic



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[1] Preliminary accounts of this work were presented at the Symposium on Sulfenyl Compounds, Intra-Science Research Foundation, Santa Monica, Calif., Nov 30, 1967 [*Quart. Rep. Sulfur Chem.*, **2**, 325 (1967)], at the Great Lakes Regional Meeting of the American Chemical Society, Milwaukee, Wis., June 14, 1968, and at the third Mechanisms Conference, Cork, Republic of Ireland, Oct 2, 1969. The manuscript originally submitted for publication on Jan 15, 1969, was withdrawn when Janice Van Horne and Professor Lamar Field, to whom the authors are deeply indebted, pointed out a serious error of misinterpretation. The present version is the result of a thorough restudy carried out during 1969–1970.

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[4] H. Fraenkel-Conrat, *J. Biol. Chem.*, **217**, 373 (1955).

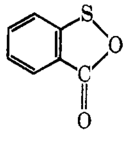
[5] L. W. Cunningham and B. J. Nuenke, *ibid.*, **234**, 1447 (1959); **235**, 1711 (1960).

[6] L. W. Cunningham and B. J. Nuenke, *Biochim. Biophys. Acta*, **39**, 565 (1960).

[7] H. Rheinboldt and E. Motzkus, *Ber. B*, **72**, 657 (1939); H. Rheinboldt and E. Mott, *ibid.*, **72**, 668 (1939).

[8] L. Field, J. L. VanHorne, and L. W. Cunningham, *J. Org. Chem.*, **35**, 3267 (1970).

[9] (a) J. P. Danehy and M. Y. Oester, *ibid.*, **32**, 1491 (1967). (b) L. Field, P. M. Giles, and D. L. Tuleen [*ibid.*, **36**, 623 (1971)] have recently



given evidence that a compound isolated by them, which decomposes in less than 1 hr, has a structure analogous to that shown here.

intermediate, as well as one or more subsequent cyclic oxidation products, if the reaction were carried out in an anhydrous medium, or one containing a minimal amount of water. When, however, an attempt was made to oxidize 3-mercaptopropionic acid in solution in glacial acetic acid by adding to it a solution of iodine in glacial acetic acid, we were surprised to find that the former would not decolorize any increment, however small, of the latter. It was soon found that all other thiols examined behaved in the same way.[10] When the ratio of thiol to iodine is sufficiently high, the absorption due to iodine in acetic acid at 478 nm[11] is all but completely replaced by much more intense absorption with maxima at 293, 360, and 740 nm, corresponding to the triiodide ion.

Starting with this unexpected result, we have made an experimental study of the reaction between 3-mercaptopropionic acid and iodine in acetic acid under anhydrous or predominantly nonaqueous conditions in the hope of shedding more light on the mechanistic pathway by which these species react.

Titration of 3-Mercaptopropionic Acid with Iodine in Anhydrous and Aqueous Acetic Acid.—It appears, then, that, while thiols are oxidized rapidly and quantitatively to disulfides by triiodide in water, in glacial acetic acid triiodide persists even in the presence of a large excess of thiol. How would these same substances behave in acetic acid as the water content of the system is gradually increased from zero?

Stock solutions were prepared of 3-mercaptopropionic acid in acetic acid of known water content and of iodine in the same solvent. Aliquots of the former were titrated to a visible end point with the latter. The results (see Table I) show clearly that the reaction of the thiol with iodine does not depend stoichiometrically upon the amount of water present; for the rapid, quantitative oxidation of the thiol to disulfide the concentration of water must be near 14 *M*. We appear to be dealing with an equilibrating system.

TABLE I

TITRATION OF 3-MERCAPTOPROPIONIC ACID WITH IODINE IN ACETIC ACID CONTAINING VARYING AMOUNTS OF WATER[a]

ml of water/100 ml of soln	Molarity of water	mequiv of I_2 consumed/mequiv of MPA
4.00	2.22	0.029
8.00	4.44	0.201
12.00	6.66	0.492
16.00	8.88	0.764
20.00	11.10	0.883

[a] 0.0450 *N* I_2 and 0.0990 *M* MPA in each case; 30-sec end points, minimally.

Ignoring for the moment the individual steps which have been postulated, it might be considered that, when iodine is added to thiol in acetic acid under titration conditions in the presence of a limited amount of water, the reaction proceeds rapidly in accord with eq 1. When eventually a point is reached, depending on the concentration of water, at which no more iodine (and triiodide) is consumed, this result cannot be attributed to depletion of water, for the concentration of water does not change significantly during the course of any of the titrations. Rather, it would seem that the system loses its ability to take up any more iodine when the effective concentration of hydrogen iodide reaches a value such that the reductive cleavage of disulfide opposes the forward reaction. The concentration of hydrogen iodide depends not only upon the amount of iodine added but upon the water content of the solvent, in accord with the equilibrium shown in eq 2.

$$HI + H_2O \xrightleftharpoons{AcOH} H_3O^+ + I^- \qquad (2)$$

If it is the basicity of water which promotes the oxidation of the thiol, then a more basic species should fulfill this function even more effectively. Table II presents data obtained by titrating solutions of the thiol in acetic acid containing known concentrations of anhydrous sodium acetate with standard iodine solutions made up in the same solvents. The results are fully in accord with the expectations based on the superior basicity of the acetate ion over that of water. When 3-mercaptopropionic acid was titrated with iodine in absolute ethanol, 0.87 equiv of iodine was required to reach an end point, corresponding to the intermediate basicity of the solvent, less than that of water, but much more than that of acetic acid.

TABLE II

TITRATION OF 3-MERCAPTOPROPIONIC ACID WITH IODINE IN ACETIC ACID CONTAINING VARYING AMOUNTS OF SODIUM ACETATE[a]

Molarity of acetate ion	mequiv of I_2 consumed/mequiv of MPA
0.12	0.890
0.24	0.945
0.36	0.970
0.48	0.962
0.60	0.957

[a] 0.0485 *N* I_2 and 0.0960 *M* MPA in each case; 30-sec end points, minimally.

Spectrophotometric Study of the System Initially. RSH–I₂–AcOH.—It may be helpful to precede a discussion of the experimental results with a summary of the conceptual framework into which the facts can be fitted. One might expect that the mixing of iodine and thiol in acetic acid would initiate reactions 3–5 and

$$RSH + I_2 \rightleftharpoons RSI + HI \qquad (3)$$

$$RSH + RSI \rightleftharpoons RSSR + HI \qquad (4)$$

$$HI + I_2 \rightleftharpoons HI_3 \qquad (5)$$

that all of them would have at least some degree of reversibility. Based on the stoichiometric summation

$$2RSH + 3I_2 \rightleftharpoons RSSR + 2HI_3 \qquad (6)$$

(eq 6) an equilibrium expression can be formulated (K_6),

$$\frac{[RSSR][HI_3]^2}{[RSH]^2[I_2]^3} = K_6$$

in which RSI and HI are not present. Alternatively, an equivalent equilibrium expression can be formulated

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[10] It has been known for a long time that hydrogen sulfide is not oxidized by iodine in solution in ethyl ether in the absence of appreciable amounts of water: (a) A. A. Noyes and G. V. Sammet, *J. Amer. Chem. Soc.*, **24**, 498 (1902); (b) L. B. Parsons, *ibid.*, **47**, 1820 (1925). Recently, Fava and coworkers have observed that "... in anhydrous hydrocarbon solvent the common oxidation of thiols by iodine fails to take place:" (c) A. Fava, G. Reichenbach, and U. Peron, *ibid.*, **89**, 6699 (1967).

[11] R. E. Buckles and J. F. Mills, *ibid.*, **75**, 552 (1953).

(K_7), based on the stoichiometric summation (eq 7), in which RSI and I_2 are not present.

$$\mathrm{RSSR} + 3\mathrm{HI} \rightleftharpoons 2\mathrm{RSH} + \mathrm{HI_3} \qquad (7)$$

$$\frac{[\mathrm{RSH}]^2[\mathrm{HI_3}]}{[\mathrm{RSSR}][\mathrm{HI}]^3} = K_7$$

Then

$$K_6K_7 = \frac{[\mathrm{HI_3}]^3}{[\mathrm{I_2}]^3[\mathrm{HI}]^3} = K_5{}^3 \qquad (8)$$

Of the three reactions 3–5, reaction 5 is the only one that can be studied independently, so that K_5 can be determined experimentally. Since reaction 6 corresponds to the situation starting with thiol and iodine, and reaction 7 to that starting with disulfide and hydrogen iodide, it was hoped that K_6 and K_7 could be evaluated experimentally. Verification of expression 8 would support the overall mechanistic view presented in the introduction.

It is necessary to consider in some detail the spectrophotometric observations made on mixtures of 3-mercaptopropionic acid and iodine dissolved in glacial acetic acid (see Table III). As quickly as they can be examined after preparation such solutions show relatively intense absorption, peaking at 293 and 360 nm, and no peak at 478 nm. The $\lambda_{\max}$ value for iodine in acetic acid is at 478 nm.[11] When equivalent amounts of iodine and of potassium iodide or hydrogen iodide in acetic acid solution are mixed, the same pattern of absorption peaking at 293 and 360 nm is observed, with a ratio of $A_{293}/A_{360} = 1.70$. Since the intensity ratios in the solutions originally containing thiol, iodine, and acetic acid are 1.69 ± 0.01 it can be concluded both, that hydrogen triiodide (or triiodide ion) is the absorbing species, and that iodine does not interfere with measurement of triiodide at 360 nm. However, examination of the spectra themselves and knowledge of molar absorptivities show clearly that triiodide ($a_m = 2.6 \times 10^4$ for hydrogen triiodide at 360 nm) would interfere seriously with measurement of iodine ($a_m = 775$ at 478 nm[11]) or of the sulfenyl iodide ($a_m = 64$ at 444 nm for 2-methyl-2-propanesulfenyl iodide in methylcyclohexane[8]).

TABLE III

SPECTROPHOTOMETRIC OBSERVATIONS OF THE REACTION BETWEEN 3-MERCAPTOPROPIONIC ACID AND IODINE IN GLACIAL ACETIC ACID AT ROOM TEMPERATURE

$[\mathrm{I_2}]_{\text{initial}}$, $M \times 10^4$	$[\mathrm{RSH}]_{\text{initial}}$, $M \times 10^4$	$\frac{[\mathrm{I_2}]_{\text{initial}}}{[\mathrm{RSH}]_{\text{initial}}}$	A_{293}	A_{360}	$[\mathrm{HI_3}]$,[a] $M \times 10^4$
1.98	8.42	0.235	0.308	0.181	0.54
4.96	10.53	0.471	1.03	0.611	1.81
3.97	4.21	0.942	0.865	0.509	1.51
4.96	4.21	1.17	0.915	0.538	1.60
4.93	2.68	1.84	0.901	0.530	1.58
9.92	4.21	2.35		0.921	2.73
4.93	1.34	3.68	0.496	0.292	0.86
9.86	2.68	3.68	1.06	0.629	1.87

[a] Values calculated on the assumption that absorption at 293 and 360 nm is attributable to $\mathrm{HI_3}$, and using a value of 2.6×10^4 for a_m at 360 nm (*vide infra*).

Considerably less than half of the iodine reacts, even when the initial molar ratio of thiol to iodine is ~4.5:1.[12] Much free iodine, then, must be present in all cases in addition to triiodide. While there is no feasible way of determining the sulfenyl iodide quantitatively, there is some evidence that at least appreciable amounts are present. When solutions are allowed to stand ~24 hr in daylight with strict exclusion of air, the absorption at 293 and 360 disappears and that at 478 increases. The photolytic disproportionation of sulfenyl iodide[7,8] could account for part of this and the extreme sensitivity of

$$2\mathrm{RSI} \xrightarrow{h\nu} \mathrm{RSSR} + 2\mathrm{HI}$$

hydrogen iodide to aerial oxidation could account for the rest of it. Later in this paper we shall present more evidence for the presence of significant amounts of sulfenyl iodide in this system.

Unfortunately, however, the information obtainable from these data, either directly or by calculation, does not permit calculation of a value for K_6. In each case original values are known for [RSH] and for $[\mathrm{I_2}]$, and values for $[\mathrm{HI_3}]$ are determined spectrophotometrically. Values for [RSH] remaining must be equal to the original [RSH] minus the $[\mathrm{HI_3}]$ found since, when an RSH disappears, either by 3 or 4, an HI appears which, in view of the large stability constant of $\mathrm{HI_3}$, is transformed almost quantitatively into the latter. However, values for $[\mathrm{I_2}]$ remaining and [RSSR] produced depend not only on the $[\mathrm{HI_3}]$ found but also upon how much of the RSI formed is subsequently consumed.

If we assume for the moment that 4 is displaced far to the left, so that very little RSSR is formed, then we may sum 3 and 5 to get

$$\mathrm{RSH} + 2\mathrm{I_2} \rightleftharpoons \mathrm{RSI} + \mathrm{HI_3} \qquad (9)$$

and

$$\frac{[\mathrm{RSI}][\mathrm{HI_3}]}{[\mathrm{RSH}][\mathrm{I_2}]^2} \cong K_9$$

Here, as above, original values are known for [RSH] and for $[\mathrm{I_2}]$, and values for $[\mathrm{HI_3}]$ are determined spectrophotometrically. Values for [RSI] may be taken equal to those found for $[\mathrm{HI_3}]$, values for [RSH] remaining may be taken equal to those for the original [RSH] minus those found for $[\mathrm{HI_3}]$, and values for $[\mathrm{I_2}]$ may be taken equal to those for the original $[\mathrm{I_2}]$ minus twice those found for $[\mathrm{HI_3}]$. The calculated values for K_9 are not included in Table III since they obviously do not constitute a constant, although the absence of a drift in one direction offers some support for the idea that relatively small amounts of disulfide are formed, and the magnitude of the values for K_9 suggests that reaction 3 goes appreciably to the right. This last idea is not necessarily at variance with the fact that more than half of the iodine has not reacted in the presence of an excess of thiol when one considers the low concentrations at which the reaction was studied.

The data for an exactly parallel study of the system initially composed of triphenylmethanethiol, iodine, and acetic acid are presented in Table IV. The only apparent

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[12] If we assume that only insignificant amounts of RSSR are formed, then the pertinent stoichiometry is $\mathrm{RSH} + 2\mathrm{I_2} \rightleftharpoons \mathrm{RSI} + \mathrm{HI_3}$ and the fraction of iodine consumed is $[\mathrm{HI_3}]/[\mathrm{I_2}]_{\text{original}}$. On the alternative assumption that only insignificant amounts of RSI persist, the relevant stoichiometry is $2\mathrm{RSH} + 3\mathrm{I_2} \rightleftharpoons \mathrm{RSSR} + 2\mathrm{HI_3}$ and the fraction of iodine consumed is $1.5[\mathrm{HI_3}]/[\mathrm{I_2}]_{\text{original}}$. For the case in which $[\mathrm{I_2}]/[\mathrm{RSH}]$ is 0.235, the fraction of iodine consumed is 0.27 on the first assumption and 0.41 on the second assumption.

TABLE IV

SPECTROPHOTOMETRIC OBSERVATIONS OF THE REACTION BETWEEN TRIPHENYLMETHANETHIOL AND IODINE IN GLACIAL ACETIC ACID AT ROOM TEMPERATURE

$[I_2]_{initial}$, $M \times 10^4$	$[RSH]_{initial}$, $M \times 10^4$	$\frac{[I_2]_{initial}}{[RSH]_{initial}}$	A_{293}	A_{360}	$[HI_3]$,[a] $M \times 10^4$
8.08	20.4	0.396	0.921	0.496	1.88
10.1	20.4	0.495	1.097	0.602	2.41
10.1	10.2	0.99	0.940	0.553	2.21
20.2	10.2	1.98	1.914	1.126	4.50
4.04	1.63	2.48	0.233	0.122	0.488
10.1	4.08	2.48	0.444	0.233	0.932

[a] Calculated on the basis given in Table III.

difference is a quantitative one: average values for K_9 are approximately 18 times greater for the primary thiol than they are for the tertiary one. This may be considered quite simply as an inductive effect; the three phenyl groups withdraw electrons from the sulfur atom and weaken its effectiveness as a nucleophile.

Spectrophotometric Study of the System Initially. RSSR–HI–AcOH.—Unless special precautions are taken the addition of small amounts of colorless, aqueous ~50% hydriodic acid to glacial acetic acid gives a brown solution within a matter of a few seconds as a result of aerial oxidation of hydrogen iodide to iodine and the transformation of substantially all of the latter to triiodide. In the present study, using freshly purified, oxygen-free acetic acid and preparing solutions in a drybox flushed with nitrogen, a stock solution, 1.44×10^{-2} M HI in AcOH, had an absorbance of only 0.016 at 360 nm 1 hr after preparation. The measured absorbances at 360 nm, then, reported in Table V, demonstrate that triiodide is formed in appreciable amounts as a result of the interaction of disulfide and hydrogen iodide, and the simplest way to interpret this fact is to assume that reactions 4, 3, and 5 have taken place in reverse, and in that order. These data corroborate the reversibility of all three reactions which we have already postulated.

TABLE V

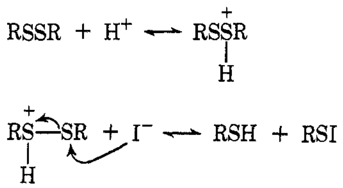
SPECTROPHOTOMETRIC OBSERVATIONS OF THE REACTION BETWEEN 3,3′-DITHIODIPROPIONIC ACID AND HYDROGEN IODIDE IN GLACIAL ACETIC ACID AT ROOM TEMPERATURE

$[HI]_{initial}$, $M \times 10^3$	$[RSSR]_{initial}$, $M \times 10^3$	A_{360}	$[HI_3]$,[a] $M \times 10^4$
3.86	7.20	0.886	3.05
1.54	7.20	0.284	0.97
0.77	7.20	0.125	0.43
3.86	1.44	0.155	0.53
1.54	1.44	0.081	0.28

[a] Calculated on the basis given in Table III.

The summation of the reverse of reactions 4, 3, and 5, as already shown, leads to the stoichiometric reaction 7 for which the equilibrium expression and constant, K_7, has already been given. However, it is not possible to use these data in Table V to calculate a value for K_7, just as it was not possible to use the data in Table III to calculate a value for K_6, and for exactly the same reason: our inability to determine the concentration of RSI upon which, in this case, both the concentration of thiol formed, and the concentration of hydrogen iodide remaining, depend. Nevertheless, the demonstration that from 5 to 10% of the hydrogen iodide added was converted to hydrogen triiodide is compatible with one or the other of two alternative interpretations. First, the disulfide might indeed be extensively cleaved (the reverse of reaction 4) and sulfenyl iodide would accumulate rather than form much thiol (reverse of reaction 3). Second, it is at least possible (if less likely) that disulfide is not extensively cleaved by hydrogen iodide.

An exactly comparable study was made of the systems consisting initially of hydrogen iodide, acetic acid, and nine other disulfides. Four of them behaved qualitatively like 3,3′-dithiodipropionic acid: 4,4′-dithiodiisobutyric acid, ethyl disulfide, isobutyl disulfide, benzyl disulfide. Four others (phenyl disulfide, *tert*-butyl disulfide, dithiodisuccinic acid, and 2,2′-dithiodipropionic acid) showed no development of absorbance beyond the blank, even after 1 hr. This means that neither triiodide nor sulfenyl iodide was formed in detectable amounts, so that no significant cleavage of these disulfides took place. It seems reasonable that in those cases in which cleavage does take place it does so by a nucleophilic displacement, assisted by electrophilic catalysis, and that one step, probably the second one, may be sterically hindered.



$$RSSR + H^+ \rightleftharpoons RS\underset{H}{\overset{+}{S}}R$$

$$\underset{H}{\overset{+}{RS}}-SR + I^- \rightleftharpoons RSH + RSI$$

Not surprisingly, the ninth compound, triphenylmethyl disulfide, despite the formal steric hindrance, is extensively cleaved by hydrogen iodide in acetic acid (see Table VI). Both the insensitivity to steric hindrance and the failure to give anything remotely resembling constancy for K_7 indicates that another mechanistic pathway pertains, and the structure suggests free-radical intermediates. Solutions of the disulfide in acetic acid at room temperature give no detectable esr signal, however, so that we have no positive evidence to support this suggestion.[13] It is a fact that this disulfide rapidly equilibrates with hydrogen iodide, as do the others which react, and it is characteristic only of this one that the absorbance developed is

TABLE VI

SPECTROPHOTOMETRIC OBSERVATIONS OF THE REACTION BETWEEN TRIPHENYLMETHYL DISULFIDE AND HYDROGEN IODIDE IN GLACIAL ACETIC ACID AT ROOM TEMPERATURE

$[HI]_{initial}$, $M \times 10^4$	$[RSSR]_{initial}$, $M \times 10^4$	A_{360}	$[HI_3]$,[a] $M \times 10^4$
5.34	4.77	0.041	0.164
10.68	4.77	0.174	0.70
26.70	4.77	1.097	4.38
26.70	9.54	1.46	5.84
5.34	23.85	0.149	0.59
10.68	23.85	0.420	1.70

[a] Calculated on the basis given in Table III.

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[13] The failure to demonstrate any esr signal is indeed surprising since F. F. Blicke [*J. Amer. Chem. Soc.*, **45**, 1965 (1923)] has reported that an initially colorless solution of tripheylmethyl disulfide in benzene becomes yellow within a few minutes and that the passage of dry air through the solution is followed by a precipitation of triphenylmethyl peroxide.

TABLE VII

SPECTROPHOTOMETRIC OBSERVATIONS OF THE REACTION BETWEEN 3-MERCAPTOPROPIONIC ACID AND IODINE IN CARBON TETRACHLORIDE AT ROOM TEMPERATURE

$[I_2]_{\text{initial}}$, $M \times 10^3$	$[RSH]_{\text{initial}}$, $M \times 10^3$	$\frac{[I_2]_{\text{initial}}}{[RSH]_{\text{initial}}}$	Time[a]	A_{517}[b]	A_{293}	A_{360}
0.98	1.047	0.94	5 min	0.084	0.018	0.004
			10 min	0.084	0.018	0.004
			5 hr	0.086	0.027	0.018
			15 hr	0.086	0.013	0.009
1.96	1.047	1.88	5 min	0.164	0.022	0.004
			10 min	0.168	0.022	0.004
			5 hr	0.172	0.022	0.013
			15 hr	0.172	0.011	0.004
4.90	1.047	4.70	5 min	0.426	0.051	0.027
			15 hr	0.423	0.029	0.004
4.90	2.10	2.35	5 min	0.426	0.066	0.029
			15 hr	0.410	0.036	0.004
4.90	4.14	1.17	5 min	0.423	0.113	0.052
			15 hr	0.410	0.078	0.018

[a] Solutions were made up in the dark, and first reading made in the dark; after 5 min solutions were kept in the light in the laboratory. [b] Values for I_2 at the same concentration in the absence of thiol were, respectively, 0.086, 0.174, 0.432, 0.432, and 0.432.

TABLE VIII

SPECTROPHOTOMETRIC OBSERVATIONS OF THE REACTION BETWEEN 3-MERCAPTOPROPIONIC ACID AND IODINE IN CYCLOHEXANE AT ROOM TEMPERATURE

$[I_2]_{\text{initial}}$, $M \times 10^3$	$[RSH]_{\text{initial}}$, $M \times 10^2$	$\frac{[I_2]_{\text{initial}}}{[RSH]_{\text{initial}}}$	Time[a]	A_{520}[b]	A_{293}	A_{360}
1.006	1.004	0.10	5 min	0.071	0.046	0.007
2.012	1.004	0.20	5 min	0.146	0.092	0.016
				0.122	0.092	0.015
5.030	1.004	0.50	5 min	0.377	0.168	0.051
			5 hr	0.314	0.161	0.043
4.024	4.016	1.00	5 min	0.328	0.081	0.011
			5 hr	0.319	0.081	0.010

[a] Solutions were made up in the dark, and first reading made in the dark; after 5 min solutions were kept in the light in the laboratory. [b] Values for I_2 at the same concentration in the absence of thiol were, respectively, 0.094, 0.187, 0.469, and 0.382.

proportional to $[HI]^2$, at least when the ratio of $[HI]/[RSSR]$ is relatively high.

The Systems, RSH–I_2, in Nonpolar Solvents.—From the data presented so far one might conclude that acetic acid inhibits the course of reactions made possible by the basicity of water. This, however, would be a mistaken conclusion. Acetic acid actually promotes the reaction, but much less effectively than water. The truth of the latter statement follows consideration of the situation in nonpolar solvents.

From the data in Tables VII and VIII, bearing in mind the high molar absorptivity of triiodide, it is barely possible to demonstrate that any triiodide is present in solutions of 3-mercaptopropionic acid and iodine in either carbon tetrachloride or cyclohexane. In cyclohexane, however, the concentrations of iodine are significantly lower in the presence of thiol than they are in its absence. And in carbon tetrachloride small amounts of a crystalline precipitate, identified as 3,3′-dithiodipropionic acid by melting point (155°) and mixture melting point, eventually appeared.

Determination of the Equilibrium Constant for the Reaction, $HI + I_2 \leftrightarrow HI_3$ in Acetic Acid.—From previously published values for the dissociation constants of the triiodide ion in water and in alcohols,[14-16] one would expect that the equilibrium constant for reaction 5 in acetic acid would be a large number. Using the "dilution technique" method of Katzin and Gebert,[16] we have found an average value of 1.1 ($\pm$0.1) $\times 10^6$ for K_5 in anhydrous acetic acid or in acetic acid containing about 0.1% water (see Table IX) and an average value of 2.6 ($\pm$0.1) $\times 10^4$ for the molar absorptivity, a_m, of hydrogen triiodide. When an identical procedure was carried out, using anhydrous potassium iodide instead of hydrogen iodide (data not included in this report), the value of a_m for the triiodide ion was only slightly larger, 2.8 ($\pm$0.1) $\times 10^4$, but the value for the dissociation constant of I_3^- was found to be significantly greater than that for HI_3: 2.8 ($\pm$0.4) $\times 10^{-5}$ for the former, and 9.2 ($\pm$0.6) $\times 10^{-7}$ for the latter (from Table IX). Recently, Guidelli and Piccardi,[17] from a study of the voltammetric behavior of the iodide–iodine couple in acetic acid at the platinum electrode, calculated values of 2.3–4.0 $\times 10^{-5}$ for the dissociation constant, in excellent agreement with our average value.

Experimental Section

Materials.—3-Mercaptopropionic acid and 2-mercaptopropionic acid, 99.2 and 99.1% thiol, respectively, by titration with aqueous potassium triiodide, and mercaptosuccinic acid, mp 154°, were gifts from Evans Chemetics, New York, N. Y. Triphenylmethanethiol, mp 107–109°, was purchased from Frinton Laboratories, Vineland, N. J. The preparation of 3,3′-dithiodipropionic acid, mp 155–156°, was described previously,[18]

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TABLE IX

DETERMINATION OF THE EQUILIBRIUM CONSTANT FOR THE REACTION, $HI + I_2 \rightleftharpoons HI_3$, IN ACETIC ACID[a]

$[I_3^-]$, $M \times 10^4$	Dilution factor, V	A_{360}[d]	r	F	$K \times 10^7$	$1/K \times 10^{-6}$	$a_m \times 10^{-4}$
4.61[b]	1	1.097					
	2	0.538	2.039	0.959	8.10	1.23	2.48
	5	0.208	5.274	0.958	8.49	1.18	2.48
	10	0.099	11.058	0.954	10.2	1.02	2.49
5.51[c]	1	1.425					
	2	0.699	2.039	0.959	9.65	1.03	2.69
	5	0.270	5.276	0.957	10.6	0.94	2.70
	10	0.128	11.13	0.962	8.27	1.21	2.68

[a] For definitions of V, r, and F, and the rationale for the method, see Katzin and Gebert.[15] $K = [HI][I_2]/[HI_3]$ so that $1/K = K_5$ in this paper. [b] Sufficient acetic anhydride was introduced to consume the water introduced with hydrogen iodide. [c] Contained ~0.1% water. [d] Values obtained with Cary spectrophotometer, 1-mm path.

and 4,4′-dithiodibutyric acid, mp 108°, 2,2′-dithiodipropionic acid, mp 110°, and dithiodisuccinic acid, mp 171–173°, were prepared in exactly the same way. The other disulfides were purchased from Distillation Products Industries, Rochester, N. Y., with the exception of triphenylmethyl disulfide. This compound, originally prepared by Vorländer and Mittag[19] by the addition of sulfuryl chloride to an alkaline alcoholic solution of triphenylmethanethiol, has apparently never been prepared by direct oxidation of the latter. That it is not feasible to oxidize the latter to the corresponding disulfide by iodine in acetic acid is obvious from the data in Table IV. But the data in Table II provided the basis for a simple and effective procedure. Triphenylmethanethiol (0.281 g) was dissolved in 100 ml of acetic acid, 0.5 M in sodium acetate. This solution rapidly consumed 1 equiv of iodine (97 ml of 1.05 N iodine) when the latter was added from a buret. The bulk of the acetic acid was removed by flash evaporation *in vacuo*, water was added, and the mixture extracted with ethyl ether. Evaporation of the ether left 0.28 g of white solid which recrystallized from chloroform, mp 160°. The highest previously reported melting point was 158°.[20]

Acetic acid was purified by the method of Tomiček and Heyrovsky.[21]

Methods.—Both a Beckman DB-G spectrophotometer and a Cary recording spectrophotometer were used, with a 1-mm light path in each case. Stable absorbance values were attained in all cases as soon as solutions were prepared.

Registry No.—Iodine, 7553-56-2; hydrogen iodide, 10034-85-2; acetic acid, 64-19-7; 3-mercaptopropionic acid, 107-96-0; triphenylmethanethiol, 3695-77-0; 3,3′-dithiodipropionic acid, 1119-62-6; triphenylmethyl disulfide, 15446-31-8; hydrogen triiodide, 30228-79-6.

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The Oxidation of Organic Divalent Sulfur by Iodine. III. Further Evidence for Sulfenyl Iodides as Intermediates and for the Influence of Structure on the Occurrence of Cyclic Intermediates in the Oxidation of Thiols

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Further support for the view that the overoxidation of certain thiols by iodine in aqueous iodide proceeds *via* a cyclic intermediate formed by the intramolecular displacement of an iodide ion from a sulfenyl iodide by a carboxylate ion is provided by the study of the oxidation of 19 selected primary and secondary thiols. Only those thiols which have a free carboxyl group on a carbon atom β or γ to the thiol sulfur atom show the marked tendency to overoxidize with decreasing initial concentration of thiol and increasing pH previously reported. 2,5-Dimercaptoadipic acid and 3-mercapto-2-(mercaptomethyl)propionic acid, in which a second mercapto group can make an intramolecular attack on the sulfenyl iodide, show a minimal tendency to be overoxidized. The view that a sulfenyl iodide is the first product of the nucleophilic attack of a thiol on iodine is strengthened by observations on two tertiary thiols, 2-mercapto-2-methylpropanoic acid and penicillamine. Though each is oxidized only to the corresponding disulfide, the deep-orange sulfenyl iodide can be seen unless the iodine is added very slowly, and significantly higher I/SH ratios are observed when iodine is added rapidly. The sulfenyl iodide corresponding to 2-mercapto-2-methylpropanoic acid has been trapped at −40° with 4-chlorothiophenol. The product of trapping, 2-(4′-chlorophenyldithio)-2-methylpropanoic acid, has been characterized.

The question of the mechanism of the oxidation of thiols by iodine has recently been reexamined in conjunction with an attempt to explain the anomalous, excessive consumption of iodine by a few thiols.[2] It was suggested that in all cases the initiating event is the nucleophilic attack of thiol (or thiolate ion) on iodine to displace an iodide ion and to form a sulfenyl iodide,

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