to be **5** (79%) and **1** (12%).

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Oxidative Cleavage and Cyclization of Disulfide Carboxylic Acids and Alcohols by Aqueous Iodine: A Facile Route to Five-Membered Ring Sultines

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The kinetics and mechanism of the oxidative cleavage by aqueous iodine of disulfide carboxylic acids and alcohols are presented. There is evidence for intramolecular interaction of the oxygen nucleophiles. The sole product of the iodine oxidation of 3,3′-dithiodipropanol is the sultine 1,2-oxathiolane 2-oxide, which is formed after the rate-determining step, apparently via rapid cyclization of the sulfenyl iodide. The anchimeric assistance provided by the neighboring carboxylate group in the reaction of 3,3′-dithiodipropanoic acid is responsible for the pH profile of the rate of oxidative cleavage. At a given pH, the rate law for the reaction is $-d[RSSR]/dt = k_I[I_3^-][RSSR](0.0905[I^-]^{-1} + 0.0019[I^-]^{-2})$. The inverse second term in iodide ion has not been observed previously in kinetic studies of disulfide reactions and is interpreted as evidence for a disulfide–iodonium complex.

Electrophilic cleavage of alkyl disulfides is facilitated by neighboring nucleophiles.[1] This facilitation may account for instances of unusually reactive disulfides in multifunctional macromolecules, such as proteins. When iodine is used as the electrophile the initially formed cyclic intermediates may be further oxidized to sulfinic and sulfonic acids. When the neighboring nucleophile is a primary amine group, unusually stable cyclic sulfinamides are generated.[1]

The kinetic study of the aqueous iodine oxidation of the amino acid cystine had been reported in the pioneering study by Shinohara and Kilpatrick.[2] Although cystine has a neighboring carboxylate group properly placed to interact with the cleaving disulfide group, the rate of cleavage is slow, and the kinetics are consistent with a mechanism in which the carboxylate group is not involved. Cleavage occurs by attack of iodide ion on a disulfide–iodine complex. However, amino acids are difficult to study because of their limited solubility in aqueous solutions and variation in overall charge. In addition, the carboxylate anion of amino acids may have reduced nucleophilicity relative to an isolated carboxylate anion due to the positive charge on the α-amino group over the pH range from 2 to 10. Therefore we decided to look for anchimeric assistance by the carboxylate group in the simplest compound with proximate disulfide and carboxylic acid groups, 3,3′-dithiodipropanoic acid. The disulfide alcohols 3,3′-dithiodipropanol and 4,4′-dithiodibutanol were also examined to see whether the weakly nucleophilic hydroxyl group would also participate in the cleavage reaction.

Experimental Section

Equipment. The equipment used has been listed in previous publications[1] except for the following. The mass spectra were determined on a V.G. Analytical high-resolution mass spectrometer with a 1250 data system. The infrared spectra were obtained from Sirius 100 and Perkin-Elmer 180 IR spectrometers.

Kinetics. The procedures and equipment have been described previously.[3]

3,3′-Dithiodipropanoic Acid. 3,3′-Dithiodipropanoic acid was obtained from Aldrich Chemical Co. and was purified by recrystallization from ethanol.

3,3′-Dithiodipropanol.[4] Thioacetamide (11.95 g, 0.159 mol) was dissolved in water containing 17.84 g (0.318 mol) of KOH. After the addition of 5.10 g (0.159 mol) of sulfur and 10.06 g (0.106 mol) of 3-chloro-1-propanol the reaction mixture was heated at 50–60 °C for 3 h. A black solid material was centrifuged out, and the remaining clear liquid was continuously extracted with ether for 24 h. The mixture was dried over $MgSO_4$, and the solvent was removed by rotary evaporation, leaving a clear viscous liquid. Vacuum distillation yielded three fractions with bp in the range 137–145 °C (0.15 torr) [lit. 160 °C (0.15 torr)]. The first and third fractions were found to contain thiols by the nitroprusside test. The middle fraction was purified further by column chromatography on Merck silica gel with 5% EtOH in $CHCl_3$. After removal of the solvent, 2.77 g of purified product was obtained: TLC (on Merck silica gel plates) R_f 0.13 (5% EtOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.7 (t, 2), 2.7 (t, 2), 1.9 (m, 2). Anal. Calcd for $C_6H_{14}O_2S_2$: C, 39.53; H, 7.74. Found: C, 39.38; H, 7.90.

1,2-Oxathiolane 2-Oxide from 3,3′-Dithiodipropanol. The disulfide (0.102 g, 5.63×10^{-4} mol) was dissolved in 10 mL of water, and the mixture was attached to an autotitrator which contained 2 M KOH. The end point was set for pH 7. The iodine (1.7×10^{-3} mol) in 3.2 mL of aqueous KI was added gradually over 4 h at ambient temperature, and the solution was allowed to stand overnight. The solution was freeze-dried, and the residue was extracted with CH_2Cl_2 in a Soxhlet extractor for 8 h. The CH_2Cl_2 was removed by slow distillation to give 0.44 g of a colorless liquid, identified as 1,2-oxathiolane 1-oxide:[5] ^{1}H NMR ($CDCl_3$) δ 4.75 (m, 1), 4.40 (m, 1), 3.05 (t, 2), 2.35 (m, 2); FT IR (neat) 1448, 1415,

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Table I. Rate Constants of Aqueous Iodine Reactions of $HO(CH_2)_3SS(CH_2)_3OH$[a]

run	10^4[RSSR]	[KI]	buffer	pH	10^4k_1, s^{-1}	k_2, M^{-1} s^{-1}
1	7.8	0.05	0.05	6.8	4.63 ± .04	0.594
2	7.8	0.10	0.05	6.8	3.40 ± .12	0.436
3	7.8	0.20	0.05	6.8	3.02 ± .06	0.387
4	7.8	0.40	0.05	6.8	1.74 ± .10	0.223
5	7.8	0.10	0.05	5.9	2.89 ± .05	0.371
6	7.8	0.10	0.05	7.8	4.18 ± 0	0.536
7	7.8	0.10	0.025	6.8	3.33 ± .06	0.427
8	7.8	0.10	0.015	6.8	3.41 ± .02	0.437
9	5.2	0.10	0.05	6.7	2.55 ± .03	0.490
10	2.6	0.10	0.05	6.7	1.31 ± 0	0.504

[a] 26.0 °C, all concentrations in molarity, phosphate buffers, $[I_3^-]_0 = (3–9) \times 10^{-5}$ M, [KI] + [KCl] = 1.0 M.

1126, 1118, 935, 727, 713 cm^{-1}; mass spectrum, m/z (relative intensity) 106.0096 (9.24), 90 (base peak, 34.69).

1,2-Oxathiolane 2,2-Dioxide. 1,2-Oxathiolane 2-oxide was dissolved in $CDCl_3$ and 1 equiv of *meta*-chloroperbenzoic acid was added. After several hours the mixture was centrifuged. The ^1H NMR of the solution had changed and now showed only three multiplets of equal integration having chemical shifts δ 4.6, 3.3, and 2.7. These values are consistent with that expected for 1,2-oxathiolane 2,2-dioxide.[6]

4,4′-Dithiodibutanol. 4-Chlorobutanol (Eastman Kodak) was converted to 4-mercaptobutanol via hydrolysis[7] of the isothiouronium salt.[8] Oxidation of the thiol with 0.3 M H_2O_2[9] yielded the disulfide, which was purified by column chromatography on Baker silica gel and elution with 5% ethanol in chloroform: TLC (on Merck silica gel plates) R_f 0.13 (5% EtOH/$CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.4 (m, 2), 3.2 (s, 1), 2.5 (t, 2), 1.4 (m, 4); mass spectrum, m/z (relative intensity) 210.0753 (53.58).

4-Sulfobutanol from 4,4′-Dithiodibutanol. The disulfide (0.210 g, 1.0×10^{-3} mol) was oxidized with aqueous iodine (3.0×10^{-3} mol) at pH 7 as described for 3,3′-dithiodipropanol. The I_2 was added over a period of 6 h. The freeze-dried residue was insoluble in CH_2Cl_2. The product had spectra consistent with 4-sulfobutanol: IR (KBr pellet) 3380 (OH), 1180, 1045 (SO_3^-) cm^{-1}; ^1H NMR (D_2O) δ 3.65 (m, 2), 2.9 (m, 2), 1.75 (m, 4).

3-Sulfopropanoic Acid from 3,3′-Dithiodipropanoic Acid. The 3,3′-dithiodipropanoic acid was oxidized with aqueous KI–I_2 at pH 7 in 4–5 h by using the same procedure as detailed above for the oxidation of 3,3′-dithiodipropanol. The resulting residue was identified as the dipotassium salt hydrate of 3-sulfopropanoic acid:[10] ^1H NMR (D_2O) δ 3.15 (m, 2), 2.65 (m, 2); IR 3400 (very broad), 2900, 1550, 1380, 1175, 1030 cm^{-1}.

3-Sulfopropanoic Acid. 3-Mercaptopropanoic acid (2 g, 0.019 mol) was added dropwise to a mixture of 14 g of 30% H_2O_2 in 14 mL of acetic acid at 50 °C. The reaction mixture was alternately heated and cooled to keep the temperature at around 50 °C for 1 h. The next day the acetic acid was removed under vacuum. The residue was converted to the barium salt by the addition of a saturated aqueous solution of $Ba(OH)_2$ until the pH was 7. The salt was separated then metathesized with an aqueous solution of K_2SO_4. The supernatant was evaporated to yield the hydrated dipotassium salt of 3-sulfopropanoic acid.[11]

Results

Products. The disulfides were oxidized at ambient temperature with aqueous KI–I_2 at pH 7 over a period of 4 h, after which iodine consumption ceased. Only one product was isolated from each of the compounds. 3,3′-Dithiodipropanol reacted with 3 molar equiv of iodine to give a 77% yield of sultine (1,2-oxathiolane 2-oxide) which had correct ^1H NMR, IR, and high-resolution mass spectra.[5,12] The sultine was further oxidized to the sultone 1,2-oxathiolane 2,2-dioxide with *m*-chloroperbenzoic acid.[6] The sultine and sultone have distinctly different ^1H NMR spectra[5,6] and can be characterized easily. The oxidation of 4,4-dithiodibutanol with 3 molar equiv of iodine in the presence of air, gave only 4-sulfobutanol. 3,3′-Dithiodipropanoic acid reacted readily with 5 molar equiv of iodine to give 3-sulfopropanoic acid which was identified by its ^1H NMR and characteristic IR.[10] The 3-sulfopropanoic acid was also prepared by H_2O_2 oxidation of 3-mercaptopropanoic acid for confirmation. Although 3-sulfopropanoic acid has been described as the product of a variety of reactions, it is usually identified as the hydrated barium salt, so it was important to prepare the material by two different methods in order to compare spectral data of the samples.

Kinetics. The kinetics were followed by monitoring the triiodide absorbance at 353 nm in a Beckman DU spectrophotometer with a Gilford update with the cell compartment thermostated at 26.0 °C. The pH was kept invariant in a given solution by use of buffer. The ionic strength was maintained by the relationship [KCl] + [KI] = 1.00 M. The reactions were pseudo-first-order in triiodide with points taken through two half-lives. In Table I are the rate data for 3,3′-dithiodipropanol. The dependence on disulfide concentration is first order (runs 8–10, log [RSSR] vs. log K_1, slope = 1.13, r = 0.997) and the observed rate constants have been divided by the disulfide concentration, which is invariant during the kinetic determinations; the rate constant is not affected by buffer concentration (runs 6–8) and is proportional to $(0.2 + [I^-])^{-1}$ (runs 1–4); $k_2 = 0.15(0.2 + [I^-])^{-1}$ M^{-1} s^{-1} is the equation for the theoretical curve. There is a small, but consistent decrease of 15–20% in the rate constant per unit decrease in pH (runs 6, 2, and 5).

The rate data for 3,3′-dithiodipropanoic acid are listed in Table II. The dependence on disulfide concentration is first order (runs 4, 7, and 8; r = 0.994, plot of log k_2 vs. log [RSSR], slope 0.85). The second-order rate constants, k_2, have been calculated by dividing k_{obsd} by [RSSR]. The rate constants are not affected by the concentration of the buffer (runs 3, 9, and 10). The rate constants are dependent on the pH and when [KI] = 0.0125 M, $k_2 = 1.94 + 24.8\,(3.2 \times 10^{-5}/(3.2 \times 10^{-5} + [H^+]))$ M^{-1} s^{-1} (r = 0.997). Additionally, the rate constants increase markedly when the concentration of iodide is decreased. An equation which predicts the iodide dependence of the rate constants has the form $k_2 = (a[I^-]^{-1} + b[I^-]^{-2})$ M^{-1} s^{-1} at pH 4.9, $a = 9.05 \times 10^{-2}$, $b = 1.9 \times 10^{-3}$, r = 0.999.

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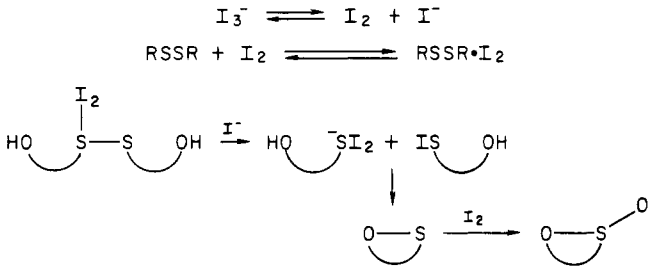
Table II. Rate Constants of Aqueous Iodine Reactions of $HOOC(CH_2)_2SS(CH_2)_2COOH$[a]

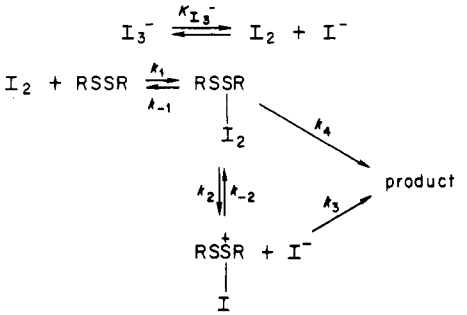
run	10^3[RSSR]	[KI]	buffer	pH	10^4k_1, s^{-1}	k_2, M^{-1} s^{-1}
1	1.0	0.0125	0.05	4.9	195 ± 4.5	19.5
2	1.0	0.025	0.05	4.9	66.3 ± 2.7	6.63
3	1.0	0.05	0.05	4.9	26.9 ± 0.3	2.69
4	1.0	0.10	0.05	4.9	8.05 ± 0.1	0.805
5	1.0	0.20	0.05	4.9	4.81 ± 0.2	0.481
6	1.0	0.40	0.05	4.9	3.01	0.301
7	0.667	0.10	0.05	4.9	6.30 ± 0.1	0.945
8	0.333	0.10	0.05	4.9	3.20	0.961
9	1.0	0.05	0.025	4.8	23.6 ± 0.3	2.36
10	1.0	0.05	0.0125	4.6	22.5 ± 0.3	2.25
11	1.0	0.10	0.05	3.9	4.93	0.493
12	1.0	0.10	0.05	5.6	10.1 ± 0.5	1.01
13	1.0	0.10	0.05	5.5[b]	9.42 ± 0.2	0.942
14	1.0	0.0125	0.05	2.8[c]	13.9 ± 1	1.39
15	1.0	0.0125	0.05	3.2[c]	33.6 ± 0.6	3.36
16	1.0	0.0125	0.05	4.1	101 ± 5	10.1
17	1.0	0.0125	0.05	5.6	246	24.6

[a] 26.0 °C, all concentrations in molarity, $[I_3^-]_0 = (3–9) \times 10^{-5}$ M, [KI] + [KCl] = 1.0 M, acetate buffer, except as noted. [b] Phosphate buffer. [c] Chloroacetate buffer.

Scheme I. Mechanism of the Oxidative Cleavage and Cyclization of 3,3′-Dithiodipropanol



Scheme II. Kinetic Scheme for the Reaction of Iodine with 3,3′-Dithiodipropanoic Acid



Discussion

Disulfide–Alcohols. The kinetic profile of the iodine oxidation of 3,3′-dithiodipropanol is $k_2 = 0.15\ (0.2 + [I^-])^{-1}$ M^{-1} s^{-1}. The form and value of k_2 is similar to that found for bis[3-(trimethylammonio)propyl]disulfide[1] ($k_2 = 0.036(0.10 + [I^-])^{-1}$ M^{-1} s^{-1} so we assume that prior to the rate-determining step the same mechanism applies in both cases. As shown in Scheme I cleavage occurs by attack of iodide ion along the S–S bond axis of the disulfide–iodine complex which is an intermediate present in steady state concentrations. Since the oxidation kinetics of 3,3′-dithiodipropanol display no anchimeric assistance, the formation of the sultine 1,2-oxathiolane 2-oxide was not expected. The neighboring hydroxyl group is not involved until after the rate-determining step and therefore cyclization possibly proceeds via both the sulfenyl iodide and the thiolate iodine complex. Oxidation of the cyclic sulfenate ester by iodine yields the observed sultine.

In our previous studies of thioether oxidations by aqueous iodine we have discovered that even when a hydroxyl group does not facilitate the oxidation, it does influence the stereochemistry of the product.[14] For example when 4-hydroxythiane is oxidized to its sulfoxide, the product is the *trans*-4-hydroxythiane 1-oxide, stereoselectively. In both these situations, the hydroxyl group must interact with the sulfur atom after the rate-determining step. The affinity of a neighboring hydroxyl group for an electrophilic sulfur atom in dilute aqueous solution is remarkable.

1,2-Oxathiolane 2-oxide is known and has been prepared under *nonaqueous conditions* via the desulfurization of the thiosulfonate,[5] the reaction of 3-mercaptopropanol derivatives with chlorine in acetic acid,[12b] and cyclic cleavage of ω-hydroxy alkyl *tert*-butyl sulfoxides.[12c] This is the first report of the generation in an *aqueous solution*. However, once formed, the sultine would be hydrolytically stable under our reaction conditions.[13] No sultine forms when 4,4′-dithiodibutanol is oxidized with aqueous iodine.

Disulfide–Acids. The sole product of the iodine oxidation of 3,3′-dithiodipropanoic acid is 3-sulfopropanoic acid. This compound had been prepared by overoxidation of 3-mercaptopropanoic acid and by reaction of 3-chloropropanoic acid with ammonium sulfite.[10,11]

The rate of reaction of 3,3′-dithiodipropanoic acid is pH dependent. The analysis indicates that at 0.0125 M iodide, the equation has the form shown in eq 1. According to

$$-\frac{d[RSSR]}{dt} = k_h[RSSR][I_3^-] \times (1.94 + 24.8(3.2 \times 10^{-5}/(3.2 \times 10^{-5} + [H^+]))) \ M^{-1}\ s^{-1} \quad (1)$$

the pH profile, the acceleration in the rate is dependent on the fraction of the compound (kinetic $pK_a = 4.5$) in the form of the carboxylate ion so the carboxylate ion must participate in the reaction prior to the rate-determining step.

At a given pH, the rate equation for the reaction has the form given in eq 2. Since there are two terms which differ in their iodide dependences, there must be two paths. In

$$-\frac{d[RSSR]}{dt} = k_I[I_3^-][RSSR](0.0905[I^-]^{-1} + 0.0019[I^-]^{-2}) \quad (2)$$

one path, the slow step involves the decomposition of a disulfide–iodine complex and corresponds to the $[I^-]^{-1}$ term in eq 2. The second path involves the decomposition of

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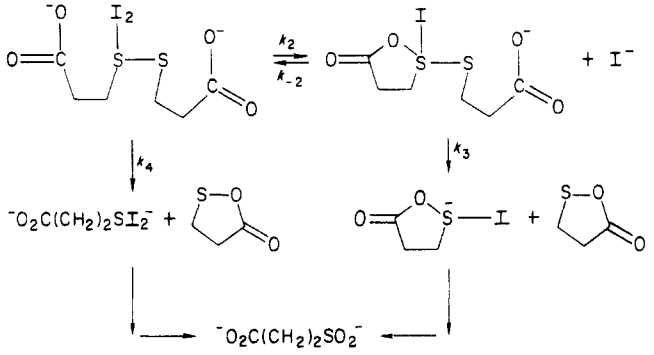
Scheme III. Role of Neighboring Carboxylate Anion in the Oxidative Cleavage of 3,3'-Dithiodipropanoate



a disulfide–iodonium complex in the slow step and corresponds to the $[I^-]^{-2}$ term in eq 2.

The kinetic scheme which generates the observed pH and iodide dependence is presented in Scheme II. The reactions of the disulfide–iodine complex and the disulfide–iodonium complex give the two-term iodide dependence as shown in eq 3. According to the pH profile

$$-\frac{d[RSSR]}{dt} = \frac{[RSSR^*][I_3^-]}{K_{I_3^-}} \frac{k_1}{k_{-1}} \left\{ k_4[I^-]^{-1} + \frac{k_1 k_3}{k_{-2}}[I^-]^{-2} \right\} \quad (3)$$

in eq 1 the portion of disulfide present in the carboxylate anionic form is more reactive, and in eq 3 [RSSR*] = [RSSR] (fraction in anionic form). The disulfide–iodine and disulfide–iodonium complexes are in equilibrium and react in rate-determining steps 4 and 3 to give the observed product. The cleavage in these complexes must occur by attack at the S–S bond by the neighboring carboxylate anion(s) in or before the rate-determining step as shown in Scheme III. Again, the lowest energy pathway presumably occurs when the nucleophile approaches along an extension of the S–S bond from the direction of the uncomplexed sulfur atom. The unusual stability of the disulfide–iodonium complex may be due to some interaction with the proximate carboxylate, but this would not lead to cleavage. Cleavage requires approach of the nucleophile at the distal sulfur. The initial products would be cyclic mixed sulfenic–carboxylic anhydrides which yield the observed sulfonic–carboxylic acid[15] on further oxidation and hydrolysis.

Sulfenic–carboxylic anhydrides have been postulated as intermediates in disproportionation reactions of mixed disulfides.[15a,b] Danehy also proposed these anhydrides as intermediates in the iodine oxidation of β-mercaptocarboxylic acids and 2,2'-dithiodibenzoate. Lacking kinetic data he postulated that the disulfide was cleaved by carboxyl participation *prior to* iodine oxidation to the sulfocarboxylic acid.[15c] The sulfinic–carboxylic anhydrides which may be intermediates in the oxidation to the sulfonic acids have also been reported.[16]

Within the range of concentrations of acid and iodide which we used for the iodine oxidation of 3,3'-dithiodipropanoic acid, the major paths are given in Schemes II and III. Reaction via iodide ion induced cleavage of the iodine complex analogous to that shown for the alcohol in Scheme I is relatively slow and would compete only at the highest iodide concentrations. At 0.4 M KI, the disulfide–carboxylic acid reacts about twice as fast as the disulfide–alcohol with aqueous iodine. Even at that concentration, the iodide ion is still not quite as effective as the neighboring carboxylate ion in attacking the iodine complex. Moreover, the rate of reaction of the disulfide–alcohol is very little affected by a decrease in the iodide concentration whereas we have observed a 65-fold increase in the rate of reaction of the disulfide–carboxylic acid when the iodide ion is decreased by a factor of 32. The increased reactivity of the disulfide–carboxylic acid is due to the increased concentration of the iodonium complex.

The iodine oxidation of 4,4'-dithiodibutanoic acid was not accelerated even in solutions containing low concentrations of iodide. Apparently, the six-membered ring sulfenic–carboxylic anhydride does not form in aqueous solution.

From these results we can now summarize the effect of a variety of neighboring nucleophiles. Acceleration of disulfide (RSSR) cleavage is the greatest when R = (dimethylamino)propyl. Some acceleration is observed with R = 2-carboxyethyl, but competition with iodide ion can occur. Although there is no kinetic effect with R = 3-hydroxypropyl, the cyclic sultine product confirms that an intramolecular reaction has occurred. Thus, the interaction of an electrophilic reagent with a disulfide bond in proteins may lead to facile bond cleavage if an amine or carboxylate anion is in proximity. In addition, amide or ester cross-linking may occur with a neighboring amine or hydroxyl group.

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