1026 *J. Org. Chem.* 1986, *51*, 1026-1029

Neighboring Group Participation in Organic Redox Reactions. 11.[1] Anchimeric Assistance by the Carboxylate Anion in Aqueous Iodine Oxidations of 3-(Alkylthio)propanoates

Joyce Takahashi Doi, Marvin H. Goodrow,[2] and W. Kenneth Musker*

Department of Chemistry, University of California, Davis, California 95616

Received September 3, 1985

The kinetics and mechanism of the aqueous iodine oxidation of three 3-(alkylthio)propanoates has been examined in detail. All the oxidations are essentially independent of external buffer and proceed via anchimeric assistance by the carboxylate anion. The reaction of aqueous iodine with both 3,3′-thiodipropanoate and 3-(methylthio)propanoate are enhanced a millionfold over that of simple thioethers, making these thioethers among the most easily oxidized of any reported. The degree of anchimeric assistance is considerably less with *N*-acetyl-*S*-methylcysteinate and is attributable to the lowered basicity of its carboxylate group.

Introduction

For several years the accelerative effect of neighboring nucleophiles on the rate of oxidation of thioethers by aqueous iodine has been examined in our laboratory. Optimal effects were initially found in appropriately substituted cyclic systems so we were somewhat surprised to find that the rate of oxidation of an acyclic thioether with a neighboring imidazole nitrogen[1] was comparable to that of the cyclic systems.

We anticipated that a similar accelerative effect might also be known for the iodine oxidation of acyclic thioethers with neighboring carboxylic acids. Glass and Wilson[3] had shown that a neighboring γ-carboxylate anion facilitates the electrochemical oxidation of the thioether group in 2,6-diendo-substituted norbornane derivatives and characterized the corresponding *O*-acyl sulfoxide salt in solution. The effect of neighboring carboxylic acids on sulfoxide reduction by HI has been examined.[4] However, only two independent studies of the iodine oxidation of an acyclic thioether in a position γ to the carboxylic acid moiety have been reported.

Higuchi and Gensch[5] stated simply, without any supporting data, that the oxidation of 4-(methylthio)butanoic acid was similar to the oxidation of tetrahydrothiophene in having similar buffer, iodide, and acid dependences. Young and Hsieh[6] were primarily interested in buffer catalysis of thioether oxidation but they did report that for the buffer-independent oxidations, the rate of oxidation of *N*-acetylmethionine was 1400 times that of *N*-acetylmethionine methyl ester. Although carboxylate participation was invoked to account for the rate enhancement, the factor of 1400 is meager when compared to the factors of 10^4–10^6 for imidazole participation. However, neither of these acyclic compounds is an ideal model to use to study carboxylate participation since a six-membered ring must form as an intermediate and the reactions are largely buffer-catalyzed. We felt that five-membered ring intermediates would form more readily than six-membered rings and the reaction would not need buffer intervention. For this reason we selected the following series of thioethers: 3-(methylthio)propanoic acid, 3,3′-thiodipropanoic acid, *N*-acetyl-*S*-methylcysteine, and thiacyclooctane-5-carboxylic acid.

Oae, Tagaki, and Ochiai[7] found that when *o*- and *p*-(methylthio)benzoic acids are oxidized by iodine in aqueous *tert*-butyl alcohol, the ortho isomer reacts much faster than the para isomer via the carboxylate anion. No details regarding the iodide dependence or the kinetics of the para isomer were given.

Experimental Section

Materials. 3-(Methylthio)propanoic Acid. To a solution of 10.6 g (0.10 mol) of 3-mercaptopropanoic acid in 15 mL of methanol and 14.8 g (0.22 mol) of KOH was added an excess (17 g, 0.12 mol) of methyl iodide. After a 1-h reflux, the solvent was removed by distillation, replaced with 15 mL of water, and acidified with 3 M H_2SO_4. Extraction of the aqueous solution with ether, followed by evaporation of the ether from the combined extracts and distillation of the residue, gave 4.5 g (38% yield) of a pale yellow oil, bp$_{13}$ 131–133 (lit.[8] bp$_{12}$ 119–123). Crystallization from hexane provided a white flaky solid, mp 20.5–21.5 °C, found to be free of impurities by GLC. ^{1}H NMR ($CDCl_3/Me_4Si$) δ 10.15 (m, 1), 2.7 (m, 4), 2.12 (s, 3).

3,3′-Thiodipropanoic Acid. Evans Chemetics, Inc., Darien, CT, graciously donated 3,3′-thiodipropanoic acid which was recrystallized from water, mp 131.0–132.0 °C.

***N*-Acetyl-*S*-methylcysteine.** Acetylation of *S*-methyl-L-cysteine (Aldrich Chemical Co., Inc.) with acetic anhydride[9] followed by acidification and continuous extraction yielded *N*-acetyl-*S*-methylcysteine: ^{1}H NMR (D_2O) δ 4.6 (m, 1, CH), 2.9 (m, 2), 2.1 (s, 3), 2.0 (s, 3). Anal. Calcd for $C_6H_{11}O_3NS$; C, 40.68; H, 6.21; N, 7.91. Found: C, 40.52; H, 6.24; N, 7.79.

Thiacyclooctane-5-carboxylic Acid. Dimethyl Bis(3-chloropropyl)malonate. Sodium, 6.4 g (0.28 mol), was dissolved in 100 mL of methanol and a mixture of 37.0 g (0.28 mol) of dimethyl malonate and 44.0 g (0.28 mol) of 1-bromo-3-chloropropane in 50 mL of ether was added. The mixture was stirred at room temperature for 48 h and then a mixture containing 0.28 mol of $NaOCH_3$ in 100 mL of methanol and 0.28 mL of 1-bromo-3-chloropropane was added. After stirring for 3 days, 500 mL of water was added and the mixture was acidified to pH 2 with 6 M HCl. Ether extraction (3 × 100 mL) followed by evaporation of the ether and fractional distillation provided 47.2 g of a viscous oil, bp 165–200 °C (20 torr), which was crystallized from methanol as needles, 21.1 g (0.074 mol, 26%): mp 39.5–40.5 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 3.72 (s, 6), 3.50 (t, 4), 2.1 (m, 4), 1.7 (m, 4); mass spectrum (70 eV), *m/z* (relative intensity) 253 (11, $M^+ - HOCH_3$), 249 (23, $M - HCl$), 225 (10, $M - HCO_2CH_3$), 208 (70, $M - ClCH_2CH_2CH_2$), 145 (91), 59 (100); IR (film) 1730 (s, C=O) cm^{-1}.

Dimethyl Bis(3-iodopropyl)malonate. A solution of 29.0 g (0.102 mol) of dimethyl bis(3-chloropropyl)malonate and 56.3 g (0.375 mol) of dried NaI in 375 mL of dry acetone was heated

---

[1] For paper 10 of this series, see: Williams, K. A.; Doi, J. T.; Musker, W. K. *J. Org. Chem.* **1985**, *50*, 4.

[2] Present address: Modesto Junior College, Modesto, CA 95350.

[3] Glass, R. S.; Duchek, J. R.; Klug, J. T.; Wilson, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 7349.

[4] Allenmark, S. *Acta Chem. Scand.* **1965**, *19*, 1.

[5] Higuchi, T.; Gensch, K.-H. *J. Am. Chem. Soc.* **1966**, *88*, 5486.

[6] (a) Young, P. R.; Hsieh, L.-S. *J. Org. Chem.* **1982**, *47*, 1419. (b) Young, P. R.; Hsieh, L.-S. *J. Am. Chem. Soc.* **1982**, *104*, 1612.

[7] Tagaki, W.; Ochiai, M.; Oae, S. *Tetrahedron Lett.* **1968**, *58*, 6131.

[8] Morradian, A.; Cavallito, C. J.; Bergman, A. J.; Lawson, E. J.; Suter, C. M. *J. Am. Chem. Soc.* **1949**, *71*, 3372.

[9] Thomson, A. E. R.; Barnsley, E. A.; Young, L. *Biochem. J.* **1963**, *86*, 145.

0022-3263/86/1951-1026$01.50/0

Table I. Spectral Data on Products

sulfoxide	IR ν_{S-O}, cm^{-1}	^{1}H NMR δ(C$_\alpha$–H), ppm
$CH_3S(-O)CH_2CH_2CO_2H$	1015	2.73 (CH_3)
$S(-O)[CH_2CH_2CO_2H]_2$	1000	3.1 (CH_2)
$CH_3S(-O)CH_2CH(NHCOCH_3)CO_2H$	1020	2.7 (CH_3)

under reflux for 8 h. The precipitated NaCl, 11.85 g (0.203 mol, 99%), was filtered and dried. The filtrate was evaporated and the residue was dissolved in CH_2Cl_2. The extract was washed with dilute $Na_2S_2O_3$. On removal of the CH_2Cl_2, 46.2 g (0.099 mol, 97%) of a white solid was obtained. Recrystallization from hexane gave white needles, mp 49.5–51.5 °C. ^{1}H NMR ($CDCl_3$/Me_4Si) δ 3.70 (s, 6), 3.11 (t, 4), 1.8 (m, 8); mass spectrum (70 eV), m/z (relative intensity) 437 (1, M - OCH_3), 409 (2, M - CO_2CH_3), 341 (100, M - I), 281 (33, M - I, HCO_2CH_3).

Dimethyl 1-Thiacyclooctane-5,5-dicarboxylate and Thiacyclooctane-5-carboxylic Acid. Employing a 2-L Morton flask containing 1 L of dry methanol and high-dilution apparatus,[10] solutions of dimethyl bis(3-iodopropyl)malonate (23.4 g, 0.0500 mol), KOH (8.25 g, 0.125 mol), and thioacetamide (3.76 g, 0.0500 mol), each made to a total volume of 150 mL with dry methanol, were added separately and simultaneously via syringe pump to the refluxing methanol over 32 h. The solvent was distilled to near dryness and 100 mL of water was added. Extraction with ether (5 × 50 mL) and workup of the combined ether extracts provided 2.85 g of a viscous yellow oil. The aqueous layer was acidified to pH 2 and extracted with ether (5 × 50 mL). The combined ether extracts produced 7.38 g of a viscous yellow oil. A portion (1.00 g) of the oil was heated under reflux with 1.5 g of potassium hydroxide in 1.5 mL of water for 3 h. The methanol was distilled and replaced with 4 mL of water followed by 2 mL of sulfuric acid. This mixture was heated for 3 h under reflux. On cooling, a viscous oil separated. The oil (0.63 g) was chromatographed on 40 g of E. Merck silica gel by eluting with a solution consisting of tetrahydrofuran, ethyl acetate, and hexane (2:15:33 mL). The material was recrystallized from hexane to give 83 mg of white needles: mp 60.5–62.0 °C; ^{1}H NMR ($CDCl_3$/Me_4Si) δ 11.15 (br, 1), 2.9 (m, 4), 2.72 (t, 1), 2.0 (m, 8); mass spectrum (70 eV), m/z (relative intensity), 176 (3, M + 2), 175 (5, M + 1), 174 (37, $C_8H_{14}O_2SO$) 173 (27, M - H), 100 (95), 41 (100); IR (KBr) 1690 (C=O) cm^{-1}.

Kinetic and Product Runs. The kinetic procedures have been described previously.[11] Separate thermostated solutions, one of the buffer, iodine, KI, and KCl and the other of the thioether, were injected into the thermostated cell and the concentration of triiodide was monitored at 353 nm. Reactions were pseudo first order in triiodide. The ionic strength was maintained by addition of KCl to the KI solution, such that [KCl] + [KI] = 1.00 M. The pK_a values were determined as described[1] in a 1.00 M KNO_3 solution. The sulfoxide products were obtained by simultaneous and dropwise addition of aqueous KI–I_2 and aqueous KOH to an aqueous solution of the thioether maintained at pH 4–7. The color of the reaction mixture became red-brown when the I_3^- was first added and was allowed to fade to pale yellow before more I_3^- was added. This method provides additional evidence for the purity of the thioethers and the rate of addition depends on the reactivity of the thioether. When an equimolar quantity of iodine had been added, the water was removed under vacuum and the residue analyzed by NMR and IR.

Results

Products. The sulfoxide products of the oxidation of the thioethers were identified by their S–O stretch in the IR and by the downfield shift of the C$_\alpha$–H in the ^{1}H NMR. These properties are listed in Table I.

The rate constants for the iodine oxidation of 3,3′-thiodipropanoic acid are listed in Table II. When [RSR′] is varied, the pseudo-first-order rate constant, k_{obsd}, is linear with [RSR′]. Thus, the second-order rate constant $k_2 = k_{obsd}/[RSR']$. The rate constant k_2 is inversely proportional to the square of the iodide ion concentration, correlation coefficient >0.999 (runs 3, 5–7, pH 4.85, Figure 1). The rate is unaffected by changes in acetate buffer concentration (runs 8–10, pH 5.8). Effect of changes in pH on k_2 are shown in Figure 2. The solid curve has been generated $(k_2)_{calcd} = 31.7K_a/(K_a + [H^+])$, using p$K_a$ = 4.7

Table II. Rate Constants of Aqueous Iodine Reactions of RSR (R = $CH_2CH_2CO_2H$)[a]

run	10^4[RSR]	[KI]	[buffer]	pH	10^4k_{obsd}, s^{-1}	k_2, M^{-1} s^{-1}
1	10.0	0.10	0.050	4.85	237 ± 6	23.7
2	7.50	0.10	0.050	4.85	174 ± 2	23.2
3	5.00	0.10	0.050	4.85	112 ± 3	22.4
4	2.50	0.10	0.050	4.85	49.5 ± 1.4	19.8
5	5.00	0.20	0.050	4.88	21.2 ± 0.4	4.2
6	5.00	0.15	0.050	4.85	41.8 ± 0.9	8.4
7	5.00	0.05	0.050	4.86	420 ± 25	84
8	5.00	0.10	0.050	5.80	146 ± 6	29.2
9	5.00	0.10	0.025	5.81	146 ± 6	29.2
10	5.00	0.10	0.0125	5.72	151 ± 14	30.2
11	5.00	0.10	0.050	3.90	22.4 ± 0.1	4.5
12	10.00	0.10	0.050	2.90[b]	2.19 ± <0.02	0.22
13	10.00	0.10	0.050	6.20	300 ± 50	30

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

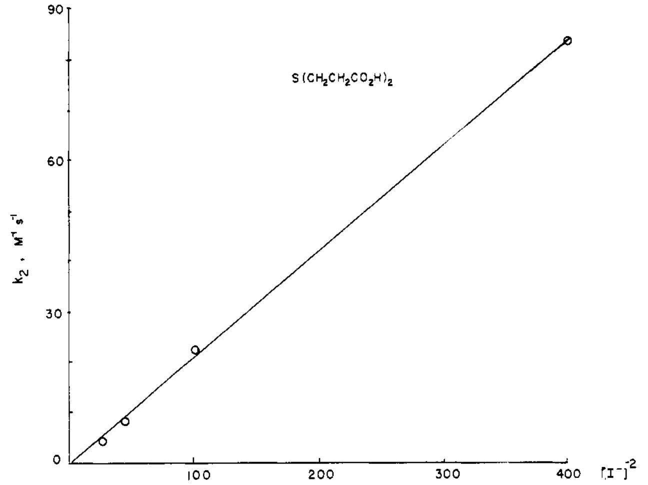


Figure 1. Second-order rate constants vs. $(1/[I^-])^2$ for the oxidation of 3,3′-thiodipropanoic acid with iodine; [RSR] = 5.0 × 10^{-4}; $[I_3^-]_0$ = (3–8) × 10^{-5} M; [KI] + [KCl] = 1.00 M; pH 4.85; 26.0 °C.

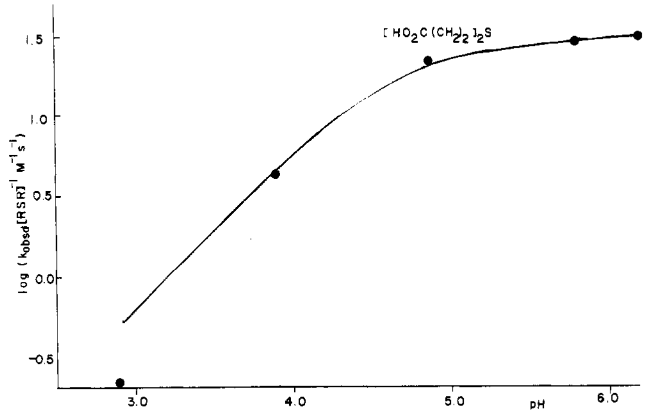


Figure 2. pH profile of the second-order rate constants for the oxidation of 3,3′-thiodipropanoic acid with iodine: [RSR] = (5–10) × 10^{-4} M; $[I_3^-]_0$ = (3–8) × 10^{-5} M; [KI] = 0.10 M; [KCl] = 0.90 M; 26.0 °C. The solid line has been calculated from the equation $(k_2)_{calcd} = 31.7K_a/(K_a + [H^+])$ where $K_a = 2 \times 10^{-5}$.

---

(10) Williams, K. A. Ph.D. Thesis, University of California, Davis, CA, 1983.

(11) Doi, J. T.; Musker, W. K. *J. Am. Chem. Soc.* **1981**, *103*, 1159.

Table III. Rate Constants of Aqueous Iodine Reactions of RSR′ (R′ = CH_3; R = $CH_2CH(NHCOCH_3)CO_2H$),[a] *N*-Acetyl-*S*-methylcysteine

run	$10^4[R^1SR]$	[KI]	[buffer]	pH	10^4k_{obsd}, s^{-1}	k_2, $M^{-1}\ s^{-1}$
1	10.0	0.00625	0.050	5.0	118 ± 5	11.8
2	6.7	0.00625	0.050	5.0	83 ± 6	12.4
3	3.3	0.00625	0.050	5.0	40 ± 1	12.1
4	10.0	0.00625	0.050	5.7	120 ± 5	12.0
5	10.0	0.00625	0.033	5.0	122 ± 4	12.2
6	10.0	0.00625	0.0167	5.0	118 ± 8	11.8
7	10.0	0.0125	0.050	5.0	35 ± 3	3.5
8	10.0	0.0250	0.050	5.0	14 ± <1	1.4
9	10.0	0.050	0.050	5.0	3.8 ± 0.2	0.38

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

Table IV. Rate Constants of Aqueous Iodine Reactions of RSR′ (R′ = CH_3; R = $CH_2CH_2CO_2H$)[a]

run	$10^4[R^1SR]$	[KI]	[buffer]	pH	10^4k_{obsd}, s^{-1}	k_2, $M^{-1}\ s^{-1}$
1	10.0	0.10	0.050	5.1	330 ± 4	33.0
2	7.50	0.10	0.050	5.1	271 ± 14	36.1
3	5.00	0.10	0.050	5.1	174 ± 3	34.8
4	2.50	0.10	0.050	5.1	79.8 ± <0.1	32.0
5	10.0	0.40	0.050	5.1	6.79 ± 0.05	0.68
6	10.0	0.20	0.050	5.1	47.4 ± 0.7	4.74
7	10.0	0.075	0.050	5.1	787 ± 18	78.7
8	10.0	0.050	0.050	5.1	2080 ± 30	208.0
9	10.0	0.10	0.050	6.2	435 ± 15	43.5
10	10.0	0.10	0.025	6.2	374 ± 25	37.4
11	10.0	0.10	0.0125	6.2	365 ± 2	36.5
12	10.0	0.10	0.050	4.2	140 ± 6	14.0
13	10.0	0.10	0.050	3.3[b]	43.0 ± 2.9	4.30
14	10.0	0.10	0.050	2.8[b]	19.8 ± 0.6	1.98
15	10.0	0.05	0.050	6.2	2400 ± 20	240.0
16	10.0	0.20	0.050	6.2	70.2 ± 0.4	7.02
17	10.0	0.40	0.050	6.2	8.08 ± 0.07	0.81

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

(3,3′-thiodipropanoic acid, reported[12] $pK_a^{\ 1} = 4.09$, $pK_a^{\ 2} = 5.08$). Thus, at a given pH,

$$-d[I_3^-]/dt = k'_1[RSR'][I_3^-][I^-]^{-2} \qquad (1)$$

Although the rate of reaction is considerably slower, the pattern of the kinetic data for *N*-acetyl-*S*-methylcysteine is similar to that for 3,3′-thiodipropanoic acid. As listed in Table III, the rate of reaction is first order in thioether; k_{obsd} vs. [RSR′] has a correlation coefficient = 0.999 (runs 1–3); it is independent of buffer concentration (runs 1, 5, 6) and inverse second order in iodide concentration: k_2 vs. $[I^-]^{-2}$, correlation coefficient, 0.999. The pK_a for *S*-methyl-*N*-acetylcysteine is 2.7 ± 0.1. Since the reaction would be reversed below pH 2 there was not a wide enough range to investigate the pH dependence. The rate law is given in eq 1.

In Table IV are listed the rate constants for the oxidation of 3-(methylthio)propanoic acid. Values of k_{obsd} decrease linearly with [RSR′], runs 1–4, correlation coefficient, 0.995; there is a slight dependence on buffer concentration, runs 9–11, and, in the pH range 2.8–6.1, k_{obsd} increases with increasing pH (runs 1, 9, 12–14). The iodide dependence (k_{obsd} vs. $[I^-]$) is −2.78, $r = 0.997$ at pH 5 (runs 1, 5–8).

However, at pH 6.1 the iodide dependence is not constant and log k_{obsd} vs. log $[I^-]$ has a slope which decreases from −2.5 to −3.1 in the range 0.4–0.05 M I^- (runs 9, 15–17). The change in iodide order did not correlate well with a simple two-term relationship between k_2 and $[I^-]$ but is described by eq 2. Plots of $[I^-]^2k_2$ vs. $(g + [I^-])^{-1}$ are shown in Figure 3. Thus, the iodide dependence is

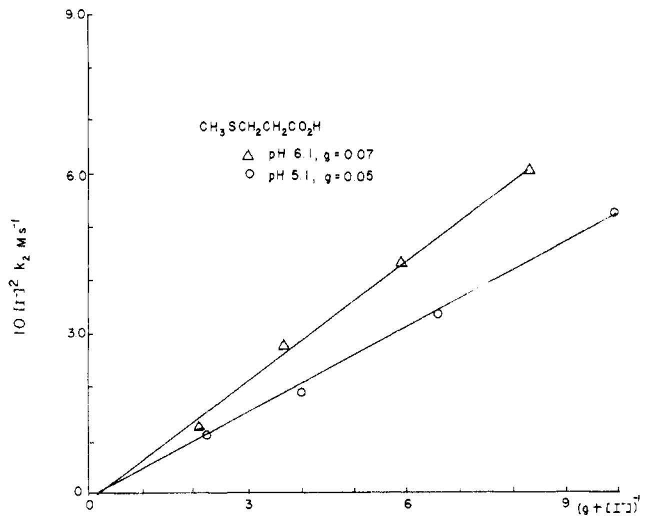
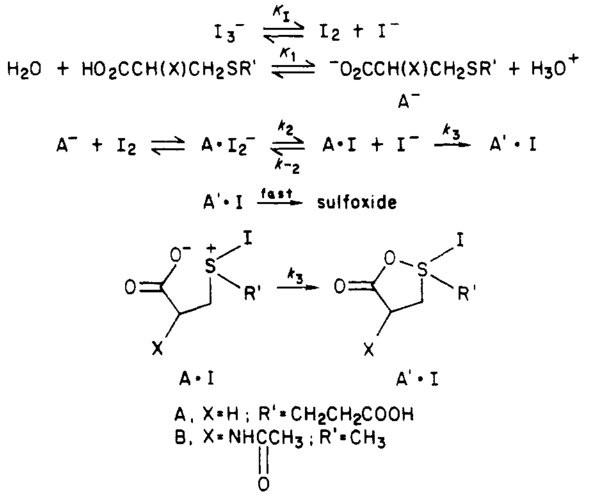


Figure 3. Plot of $10[I^-]^2k_2$ M s^{-1} vs. $(g + [I^-])^{-1}$ for the oxidation of 3-(methylthio)propanoic acid with iodine: [RSR] = 10×10^{-4} M; $[I_3^-]_0 = (3–8) \times 10^{-5}$ M; [KI] + [KCl] = 1.00 M; (○) pH 5.1; (△) pH 6.2.

Scheme I. Mechanism for the Aqueous Iodine Oxidation of 3,3′-Thiodipropanoic Acid and *N*-Acetyl-*S*-methylcysteine



$$-d[I_3^-]/dt = k''_i[RSR'][I_3^-][I^-]^{-2}(g + [I^-])^{-1} \qquad (2)$$

where $g = 0.05$ at pH 5.1 and 0.07 at pH 6.1.

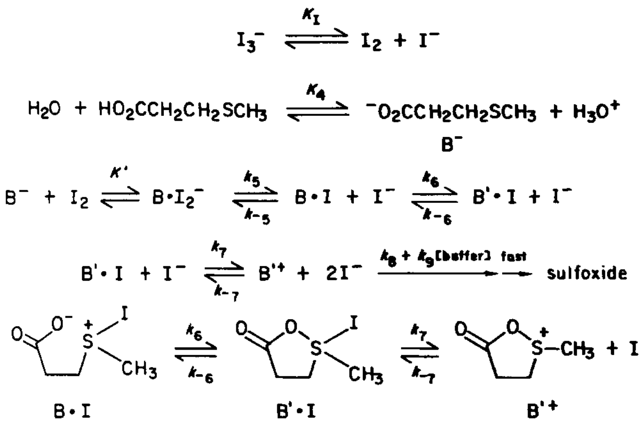
Discussion

The oxidation of 3-thiodipropanoic acid to the sulfoxide by iodine occurs extremely rapidly, is buffer independent, and, at a given pH, proceeds according to the rate law given in eq 1. The same behavior was displayed in the iodine oxidation of 1-methyl-2-[3-(methylthio)propyl]imidazole.[1] When the data for both compounds are normalized for their base forms, they are oxidized at almost the same rate by aqueous iodine, making them the most rapidly oxidized acyclic thioethers known. Acyclic thioethers having either a neighboring imidazole or a carboxylic acid group must oxidize according to a similar mechanism prior to the rate-determining step. As shown in Scheme I, iodine and the 3-thiodipropanoate anion form a complex $A{\cdot}I_2^-$ which ionizes to the iodosulfonium ion A·I. Cyclization by the neighboring nucleophile gives A′·I in the rate-determining step. The concentration of iodosulfonium ion A·I is governed not by K_1, the dissociation constant for A, but rather

---

[12] Kortüm, G.; Vogel, W.; Andrussow, K. *Pure Appl. Chem.* **1960**, *1*, 187.

Scheme II. Mechanism for the Aqueous Iodine Oxidation of 3-(Methylthio)propanoic Acid



by the acid dissociation constant of A·I, which is the kinetic K_a.

N-Acetyl-*S*-methylcysteine is oxidized by aqueous iodine to its sulfoxide at a much slower rate which is buffer-independent and pH-independent at acid concentrations lower than the K_a of the carboxylic acid and has a rate law similar to 3,3′-thiodipropanoic acid. 3,3′-Thiodipropanoic acid is a considerably weaker acid than *N*-acetyl-*S*-methylcysteine, so that intramolecular catalysis by the carboxylate group (Scheme I, k_3) is more effective. Prior to the rate-determining step, *N*-acetyl-*S*-methylcysteine also displays the behavior shown in Scheme I. Its homologue, *N*-acetylmethionine (NAM),[6a] has been studied extensively but its rate is accelerated by buffer. However, the buffer-independent rate of NAM has the same rate law as *N*-acetyl-*S*-methylcysteine but NAM reacts about 6 times more slowly. Indeed, if NAM is oxidized 1400 times more rapidly than its methyl ester (NAME),[6b] then *N*-acetyl-*S*-methylcysteine reacts 9000 times faster than NAME. The acceleration of *N*-acetyl-*S*-methylcysteine over NAM is attributable to the more rapid formation of the five- vs. the six-membered ring intermediate. At the levels of buffer concentration used here, intramolecular cyclization by carboxylate to give an *O*-acyl sulfoxide is more rapid than intermolecular *O*-acyl sulfoxide formation by the acetate ion used as the buffer.

Sulfoxide is formed by the aqueous iodine oxidation of 3-(methylthio)propanoic acid at a rapid rate which is pH-dependent and very slightly buffer dependent and, at invarient pH and buffer, has the rate law given in eq 2. While this kinetic behavior is different from that of 3,3′-thiodipropanoic acid, it is similar to that of 1,5-dithiacyclooctane (DTCO)[11] except that DTCO has virtually no pH dependence. The pH dependence of 3-(methylthio)propanoic acid is due to the requirement for a free carboxylate ion which is responsible for the intramolecular reaction as shown in Scheme II. Iodine reacts with the thioether to form the complex $B{\cdot}I_2^-$ which is in equilibrium with the iodosulfonium ion, B·I. The cyclic iodosulfurane, B′·I passes through the steady-state intermediate B'^+ to give the sulfoxide. A small amount of buffer catalysis occurs in decomposition of B'^+ and is shown as k_9[buffer]. According to the steady-state principle

$$k_{\mathrm{obsd}} \propto \frac{[k_8 + k_9(\mathrm{buffer})]/k_{-7}}{[\mathrm{I}^-]^2[\mathrm{I}^-] + \dfrac{k_8 + k_9(\mathrm{buffer})}{k_{-7}}} = \frac{g}{[\mathrm{I}^-]^2([\mathrm{I}^-] + g)}$$

with $[k_8 + k_9(\mathrm{buffer})]/k_{-7}$ having the values of 0.05 and 0.07 at pH 5.1 and 6.1, respectively.

Allenmark[4] previously reported that the reduction of the sulfoxide of 3-(propylthio)propanoic acid by iodide (2.0 M $HClO_4$, 0.2 M I^-, 25 °C) occurs with a half-life of 19 min. Under these conditions the rate of reduction is proportional to $[H^+][RS(O)CH_2CH_2CO_2H]$ and the iodide dependence suggests that a *O*-acyl sulfoxide ion may be the intermediate present in steady-state concentrations. In the iodine oxidation of 3-(methylthio)propanoic acid, the data are consistent with *O*-acylsulfoxide ion, B'^+ (Scheme II), as a steady-state intermediate. Thus the two reactions are consistent with the principle of microscopic reversibility.

When comparing the kinetic behavior of 3,3′-thiodipropanoic acid with 3-(methylthio)propanoic acid it is important to realize that for the former, the inverse second-order dependence in iodide ion (eq 1) is based on the same rate law as the latter (eq 2) if $g = [k_8 + k_9(\mathrm{buffer})]/k_{-7}$ is much larger than $[\mathrm{I}^-]$. In that case $g/([\mathrm{I}^-]^2([\mathrm{I}^-] + g))$ approaches $1/[\mathrm{I}^-]^2$. The most probable explanation for the larger value of g for the dicarboxylic acid than for the monocarboxylic acid would be that the second carboxylate group hastens the cleavage of the *O*-acylsulfoxide salt A′·I (Scheme I) either via anhydride formation[6] by intramolecular attack of the carboxylate anion at the carbonyl carbon or via attack on the sulfur to form a diacyloxyspirosulfurane.[13] Both of these intermediates would then undergo rapid hydrolysis to the sulfoxide.

Cursory experiments with a mesocyclic analogue, thiacyclooctane-5-carboxylic acid, indicate that the aqueous iodine oxidation of this thioether proceeds without anchimeric assistance by the carboxylate group. Apparently the [3.3.2]bicyclodecane intermediate is not readily formed because of poor alignment between the carboxylate anion and sulfur.

At pH 5, 0.01 M KI, several thioethers can easily be compared because their rates of reaction are proportional to $[\mathrm{I}^-]^{-2}$. Their relative rates (corrected for buffer effects when necessary) are as follows: 3,3′-thiodipropanoate:*N*-acetyl-*S*-methylcysteinyl anion:*N*-acetylmethionyl anion[6]:*N*-acetylmethionine methyl ester[6] = (7×10^6):(8.4×10^3):(1.4×10^3):1. Of the 3-(alkylthio)propanoates, the lowered reactivity of the *N*-acetyl-*S*-methylcysteine is due largely to the lowered basicity of the anion. Thus 3,3′-thiodipropanoate and 3-(methylthio)propanoate are among the most easily oxidized thioethers known.

Acknowledgment. We acknowledge the assistance of Barry Silken and Jeffery D. Beller in the preliminary stages of this research.

Registry No. 3-Mercaptopropionic acid, 107-96-0; 3-(methylthio)propanoic acid, 646-01-5; 3-thiodipropanoic acid, 111-17-1; *N*-acetyl-*S*-methylcysteine, 16637-59-5; 1-bromo-3-chloropropane, 109-70-6; bis(3-chloropropyl)malonate, 83103-72-4; dimethyl bis(3-iodopropyl)malonate, 100166-57-2; dimethyl malonate, 108-59-8; dimethyl 1-thiacyclooctane-5,5-dicarboxylate, 100166-58-3; thiacyclooctane-5-carboxylic acid, 100166-59-4; 3-(methylsulfinyl)propanoic acid, 14090-85-8; 3-sulfinyldipropanoic acid, 3680-08-8; *N*-acetyl-*S*-methylcysteine sulfoxide, 16637-63-1.

---

[13] Kapovits, I.; Rabai, J.; Ruff, F.; Kucsman, A. *Tetrahedron* 1979, *35*, 1869.