THE JOURNAL OF Organic Chemistry

VOLUME 50, NUMBER 1

JANUARY 11, 1985

A General Mechanism for the Oxidative Cleavage of Amine Disulfides and Cystine in Aqueous Iodine.[1] Isolation of Cyclic Sulfinamides

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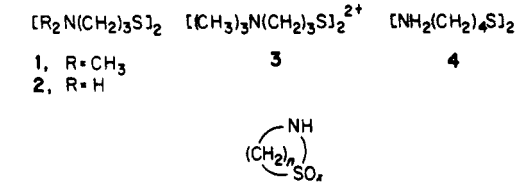
Received August 30, 1984

When disulfides are cleaved by aqueous iodine, neighboring group participation facilitates the rate of reaction and the formation of cyclized products. The series of bis-disulfides $[X(CH_2)_3S]_2$ was prepared, X = $N(CH_3)_2$, 1, NH_2, 2, $N(CH_3)_3^+$, 3, as well as $[NH_2(CH_2)_4S]_2$, 4. The tertiary amine, 1, is oxidized by aqueous I_2 at a rate which is accelerated by as much as 10^6 over the rate of reaction of the quaternary ammonium iodide salt 3. The oxidation products of 1 are the sulfinic and sulfonic acids while 3 yields the sulfonic acid. Aqueous iodine reacts with the primary amines 2 and 4 at moderately accelerated rates to give the cyclic sulfinamides, isothiazolidine 1-oxide from 2 and tetrahydro-1,2-thiazine 1-oxide from 4. This oxidative cyclization reaction is the most direct route to these cyclic sulfinamides. At a given pH, the rate law for the oxidation of 1 and 2 is $-d[RSSR]/dt = -k[RSSR][I_2]$. At high pH, compound 4 has the same rate law. The kinetic data for 4 at low pH and for 3 resemble those reported in a classical study of the aqueous iodine oxidative cleavage of cystine.[2] The kinetics and mechanisms of these reactions will be discussed.

Introduction

The formation and cleavage of disulfides is important in many areas of chemistry and biochemistry. The facilitation of electrophilic cleavage by neighboring nucleophiles may account for the unusual reactivity of disulfides in proteins. We recently reported[1] an enhancement of 10^6 in the rate of reaction of bis[3-(dimethylamino)propyl] disulfide, 1, with aqueous I_2 over that of cystine or of the



5, $n=3$; $x=1$
6, $n=4$; $x=1$
7, $n=4$; $x=2$

bis quaternary ammonium iodide salt of bis[(3-trimethylammonio)propyl] disulfide, 3. To account for the acceleration, we proposed a cyclic cationic intermediate which subsequently was cleaved to give a mixture of sulfinic and sulfonic acids. We reasoned that the primary amine disulfides, bis(3-aminopropyl) disulfide, 2, and bis(4-aminobutyl) disulfide, 4, would also cyclize, but these cyclic intermediates could be deprotonated and oxidized to cyclic products.

Experimental Section

Equipment. The equipment has been listed in previous publications[3] except for the following. The high resolution mass spectra were determined on a DuPont 492 spectrometer. The FT-IR spectra were obtained by using a Nicolet MX1 spectrometer.

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

Synthesis. Bis[3-(dimethylamino)propyl] Disulfide (1) and Bis[3-(trimethylammonio)propyl] Disulfide (3). The preparation and properties of compounds 1 and 3 have been described.[1]

Bis(3-aminopropyl) Disulfide (2). Compound 2 was prepared from 3-chloro- or 3-bromopropylamine hydrochloride (Aldrich) by using sodium thiosulfate in 50% aqueous methanol and refluxing for one day.[4] The refluxing was continued as the solution of iodine in methanol was added dropwise. The methanol was removed under vacuum, and the aqueous solution was made basic with NaOH and continuously extracted with $CHCl_3$. The $CHCl_3$ was removed under vacuum and the pale yellow residue was distilled: bp 110 °C (0.2 torr); ^1H NMR ($CDCl_3$) δ 2.7 (m, 8), 1.7 (m, 4); dipicrate mp 155–156 (lit.[4c] 145–146). Anal. Calcd

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0022-3263/85/1950-0001$01.50/0

Table I. Rate Constants of Aqueous Iodine Reactions of 2[a]

	10^4[RSSR]	[KI]	buffer	pH	10^4k_1, s^{-1}	k_2, M^{-1} s^{-1}
1	9.70	0.2	0.050	5.8	13.1	1.35
2	4.80	0.2	0.050	5.8	7.92	1.65
3	2.40	0.2	0.050	5.8	5.03	2.09
4	1.20	0.2	0.050	5.8	2.25	1.88
5	4.80	0.8	0.050	6.0	4.3 ± 0.2	0.90
6	4.80	0.6	0.050	6.0	5.8	1.21
7	4.80	0.4	0.050	6.0	7.3 ± 0.2	1.52
8	4.80	0.2	0.050	6.0	16 ± <1	3.33
9	4.80	0.1	0.050	6.0	25 ± 1	5.21
10	4.80	0.2	0.050	7.0	102 ± 5	21.3
11	4.80	0.2	0.050	8.25	940 ± 30	196
12	4.80	0.2	0.031	7.0	100 ± 7	20.8
13	4.80	0.2	0.012	7.0	100 ± 6	20.8

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

for $C_{18}H_{22}N_8S_2O_{14}$: C, 33.8; H, 3.45; N, 17.55. Found: C, 33.99; H, 3.52; N, 17.46.

Bis(4-aminobutyl) Disulfide (4). Compound **4** was prepared as the dihydrobromide salt by the method of Dirscherl:[5] ^{1}H NMR (D_2O) δ 2.95 (m, 4), 2.7 (m, 4), 1.7 (m, 8); mp 231–233 (lit.[5] mp 240). Anal. Calcd for $C_8H_{22}N_2S_2Br_2$: C, 26.0; H, 6.0; N, 7.6. Found: C, 25.3; H, 5.76; N, 7.29.

Isothiazolidine 1-Oxide (5) from 2. Disulfide **2**, 0.47 g (0.0026 mol), was dissolved in 50 mL of water and the mixture was attached to the autotitrator which contained 1.0 M KOH. The endpoint was set at pH 7. The iodine, 2.5 g (0.0084 mol) in 25 mL of methanol was added 1–2 mL at a time over a period of 2 h at ambient temperature. The solution was filtered, and the solvent was removed, first by rotoevaporation, then by freeze drying. The off-white, hygroscopic residue was evaporated to a dry powder after treatment with ethanol. Soxhlet extraction of the powder with $CHCl_3$ and removal of the solvent yielded a colorless liquid which was column chromatographed on 9 g of Merck silica gel with 5% ethanol in $CHCl_3$. The organic product was collected in eluent volumes of 60–140 mL. After the solvent was distilled, the 0.2 g of residual liquid was purified by GLC with a 6 ft SE-30 glass column at 130 °C: ^{1}H NMR ($CDCl_3$) δ 4.5 (br, 1), 3.7 (m, 1), 3.1 (m, 1), 2.8 (m, 2), 2.3 (m, 2); IR (neat) 3225, 1048, 1014, 640 cm^{-1}; IR (CCl_4) 3240, 1065, 1010 cm^{-1}; mass spectrum, m/z 105.02785 (58.04).

Tetrahydro-1,2-thiazine 1-Oxide (6) and Tetrahydro-1,2-thiazine 1,1-Dioxide (7) from 4. The disulfide **4**·2HBr, 0.44 g (0.0012 mol), was dissolved in 20 mL of water and the procedure used for the reaction of **2** was followed. The methanol solution of iodine, 0.93 g (0.0037 mol), was added over 3 h. The mixture of products was found in the first 60 mL of eluent from the silica gel column. The residue, 0.1 g, was analyzed and purified by GLC, yielding two fractions, **6**, mp 42 °C, and **7**, mp 105 °C (lit.[5] mp 115 °C), in the ratio 3:1. Compound **6** was characterized as follows: ^{1}H NMR ($CDCl_3$) δ 3.35 (m, 2), 2.85 (m, 1), 2.65 (m, 2), 2.1 (m, 2), 1.7 (m, 2); IR (CCl_4) 3230, 1535, 1075, 1040 cm^{-1}; mass spectrum, m/z 119.04095 (57.02). Compound **7** was characterized as follows: ^{1}H NMR ($CDCl_3$) δ 3.3 (m, 2), 3.0 (m, 2), 1.5 (m, 2);[6] IR (KBr pellet) 3240, 1287, 1115 cm^{-1}. This spectrum corresponds to that of Figure 1, ref 5 and indicates that the figure legends in ref 5 are reversed. Mass spectrum, m/z 135.0384 (49.26).

Results

Products. The products of the reactions were identified by ^{1}H NMR and IR. For new compounds, a high-resolution mass spectrum was obtained. The only compound isolated from the oxidation of **2** with 3.8 molar equiv of iodine is isothiazolidine 1-oxide, **5**. Compound **4** reacts with 3.0 molar equiv of iodine to give both tetrahydro-1,2-thiazine 1-oxide, **6**, and 1,2-thiazine 1,1-dioxide, **7**, in the ratio of 3:1. The products from **1** and **3** have been reported previously.

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Table II. Rate Constants of Aqueous Iodine Reactions of 4[a]

	10^4[RSSR]	[KI]	[buffer]	pH	10^4k_1, s^{-1}	k_2, M^{-1} s^{-1}
1	3.97	0.20	0.05	7.0	5.6	1.4
2	3.97	0.20	0.031	7.0	5.7 ± 0.1	1.4
3	3.97	0.20	0.0125	7.0	5.7 ± 0.2	1.4
4	8.51	0.10	0.05	7.0	22.0 ± 0.3	2.6
5	5.70	0.10	0.05	7.0	14 ± 2	2.5
6	2.85	0.10	0.05	7.0	7.2 ± 0.7	2.5
7	3.97	0.20	0.05	5.9	2.8 ± 0.1	0.71
8	3.97	0.10	0.05	5.9	3.6 ± 0.1	0.91
9	3.97	0.05	0.05	5.9	4.12	1.04
10	3.97	0.80	0.05	5.9	2.15	0.54
11	4.48	0.80	0.05	7.9	21.9 ± 0.1	4.9
12	4.48	0.40	0.05	7.9	43 ± 2	9.6
13	4.48	0.20	0.05	7.9	74 ± 1.3	16.5
14	4.48	0.10	0.05	7.9	99.1 ± <0.1	22.1
15	4.48	0.05	0.05	7.9	199 ± 4	44.4

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

Table III. Rate Constants of Aqueous Iodine Reactions of 3[a]

	10^4[RSSR]	[KI]	buffer	pH	10^4k_1, s^{-1}	k_2, M^{-1} s^{-1}
1	5.58	0.10	borate	9.2	1.0	0.18
2	5.58	0.05	borate	9.2	1.3	0.23
3	5.58	0.025	borate	9.2	2.1	0.28
4	5.58	0.0125	borate	9.2	1.8	0.33
5	5.58	0.10	borate	8.2	1.2	0.21
6	5.58	0.20	phos	7.9	1.2	0.21
7	5.58	0.20	phos	6.9	0.90	0.16
8	5.58	0.20	phos	5.9	0.68	0.12
9	3.72	0.20	phos	7.9	0.68	0.18
10	1.86	0.20	phos	7.9	0.40	0.22

[a] 26.0 °C, all concentrations in molarity, $[I_3^-]_0 = (3–9) \times 10^{-5}$ M, 0.05 M buffer, [KI] + [KCl] = 1.0 M.

Kinetics. The kinetics are followed by monitoring I_3^- absorbance at 353 nm in a Beckman DU spectrophotometer with a Gilford update with the cell compartment thermostatted at 26.0 °C. Within a given run the pH was invarient due to phosphate or borate buffer. When the concentration of KI was varied, the ionic strength was maintained by addition of KCl such that [KCl] + [KI] = 1.00 M. The reactions are pseudo-first-order in triiodide with correlation coefficients of 0.994 for points taken through 75% reaction. In Table I are the rate data for **2**. The dependence on disulfide concentration is first order (runs 1–4, log [RSSR] vs. log k_1, slope = 0.83, r = 0.992); there is an inverse first-order dependence in iodide ion concentration (runs 5–9, log [I^-] vs. log k_2, slope = –0.80, r = 0.992); there is no buffer dependence (runs 11–13) and in 0.20 M KI, the rate constant, k_2, follows the equation $k_2 = 0.83 + (1.25 \times 10^8)[OH^-]$ M^{-1} s^{-1} (runs 8, 10, 11).

In Table II are the rate data for **4**. The dependence on disulfide concentration is first order (runs 4–6, [RSSR] vs. k_1, r = 0.999); at pH 8 there is an inverse first-order dependence in iodide concentration (runs 11–15, k_1 vs. $[I^-]^{-1}$, r = 0.993); at pH 5.9, the dependence on [I^-] has two terms and the rate constant $k_2 = (0.026[I^-]^{-1} + 1.2([I^-] + 2)^{-1})$ M^{-1} s^{-1} (runs 7–10). The iodide dependence is shown in Figure 1 where the solid line has been drawn through the values predicted from the equation. There is no buffer dependence (runs 1–3) and in 0.20 M KI, the rate constant, k_2, follows the equation, $k_2 = 0.5 + 1.7 \times 10^7$ $[OH^-]$ M^{-1} s^{-1}.

In Table III are the rate data for **3**. The dependence on disulfide concentration is first order (runs 6, 9, 10), $k_2 = k_{obsd}/[RSSR] = (0.20 \pm 0.02)$ M^{-1} s^{-1}. When the pH is decreased from 7.9 to 5.9 there is a small decrease in the rate constant from 0.21 to 0.12 M^{-1} s^{-1} (runs 6–8). The rate constant $k_2 = 3.6 \times 10^{-2}$ $([I^-] + 0.10)^{-1}$ M^{-1} s^{-1} at pH 9.2

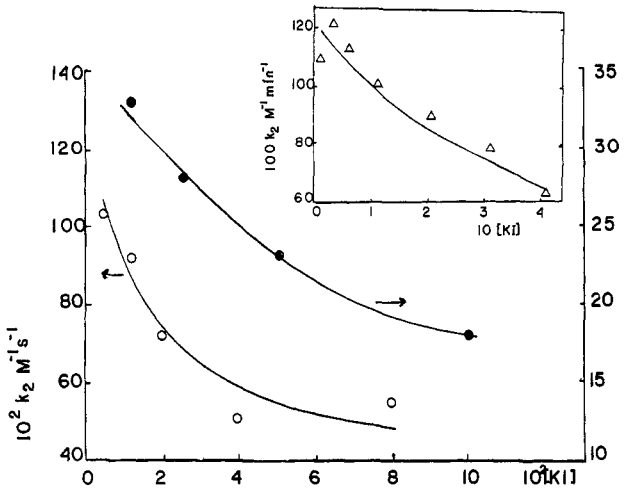


Figure 1. Iodide dependence of the rate constants, k_2, for **4**, **3**, and cystine: (○) $[NH_2(CH_2)_4S]_2$, **4**, pH 5.9; (—) from the equation $k_2 = 0.026\,[I^-]^{-1} + 1.2([I^-] + 2.0)^{-1}$ M^{-1} s^{-1}; (●) $[(CH_3)_3N(CH_2)_3S]_2^{2+}$, **3**, pH 9.2; (—) from the equation $k_2 = 0.036\,([I^-] + 0.10)^{-1}$ M^{-1} s^{-1}. Insert: (△) $[S\text{-}CH_2CH(NH_2)(CO_2H)]_2$, Shinohara's data;[2] (—) from the equation $k_2 = 0.61\,([I^-] + 0.5)^{-1}$ M^{-1} min^{-1}.

(runs 1–4). The equations for the iodide dependence were used to generate the solid lines in Figure 1.

Discussion

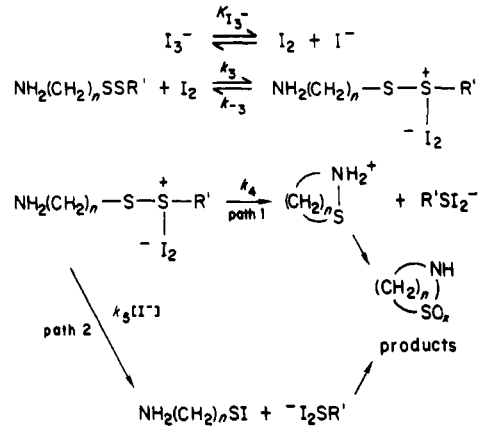
Products. The cyclization products which are isolated are unusual because they are sulfinamides, rather than sulfonamides (sultams) and they are isolated from aqueous solution. Previous workers had shown that when **4** was treated with aqueous chlorine or bromine in a 1:5 molar ratio, the initial products were the sulfonyl halides which, in turn, cyclized to the sultam, either thermally, or on treatment with aqueous base. In contrast, only sulfonyl halides were formed on treatment of **2** with aqueous chlorine or bromine; no cyclic products were reported.[7] When **2** was treated with 30% H_2O_2 with a trace of KI as an indicator, 3-aminopropanesulfinic acid was obtained.[8] Thus, the reactions of **2** and **4** with other common oxidizing agents lead directly to the sulfonyl halide or to the sulfinic acid.

A different type of cyclization by neighboring amide is achieved when chlorine is treated with 3,3′-dithiobis[propionamide] in a 3:1 molar ratio in either toluene, ethylene dichloride, or ethyl acetate.[9] The initially formed 4-isothiazolidin-3-one reacts further to yield 5-chloro-4-isothiazolin-3-one and 3-hydroxyisothiazole.

Compounds **5** and **6** are listed as intermediates in the preparation of cyclic sulfonimidates, $(CH_2)_nNS(O)(OAr)$, where they were synthesized by the BuLi cyclization of ω-chloroalkanesulfinamides in THF.[10] No experimental details or physical properties of these intermediates have been published.

Acyclic sulfinamides are commonly prepared by ammonolysis of sulfinyl chlorides in methylene chloride at −20 to −40 °C.[11] Typical IR bands are at 1070–1010 and 700–660 cm^{-1}. They decompose at temperatures above 90 °C. In contrast, compounds **5** and **6** have been prepared at ambient temperature in aqueous solution and are purified by GLC at 130 and 160 °C.

Scheme I. Mechanism of the Aqueous Iodine Cleavage of 2 and 4



Kinetics. For the cleavage of **2**, the rate law is similar to that of the tertiary amine disulfide, **1**, and is given in eq 1.

$$k_{obsd} = k[RSSR][I^-]^{-1}\{a + b[OH^-]\}\ M^{-1}\ s^{-1} \quad (1)$$

If $K_{I_3^-}$ is the equilibrium constant for triiodide formation, the rate of triiodide consumption is described in eq 2. The

$$d[I_3^-]/dt = -k[RSSR][I_2]K_{I_3^-}\{a + b[OH^-]\}\ M^{-1}\ s^{-1} \quad (2)$$

rate law contains the term $b[OH^-]$ which is proportional to the concentration of free amine present over the range of pH from 5.8 to 8.2. It is this portion of the reaction which results in the rate acceleration at higher pH and is due to the participation of the free amine in the cyclization reaction. There is an additive term "a" which would account for a reaction which proceeds via the total disulfide. At pH 8, compound **4** has a rate law of the same form. The kinetic scheme for the reaction with neighboring group participation was described in our report[1] on **1**. This scheme is shown as path 1 in Scheme I. The first cyclic intermediate is a protonated sulfenamide which is subsequently deprotonated and oxidized. Thus, a cyclic sulfinamide was isolated from **2** and a mixture of sulfinamide and sulfonamide from **4**.

For **4** at pH 6, the rate constant $k_2 = \{0.026[I^-]^{-1} + 1.2([I^-] + 2)^{-1}\}$ M^{-1} s^{-1}. The first term, $0.026[I^-]^{-1}$, results from the reaction proceeding by path 1 of Scheme I. The second term, $1.2([I^-] + 2)$, could be obtained from the reaction proceeding by path 2 in Scheme I, provided that iodide ion attacks the disulfide–iodine complex which is present at steady-state concentration. A more thorough discussion of path 2 will be given in the discussion of the kinetics of the quaternary ammonium salt **3** which follows.

A very thorough kinetic study of the oxidative cleavage of cystine to cysteic acid by aqueous iodine was reported by Shinohara and Kilpatrick.[2] In their introduction they state that the rate-determining step "is the reaction between a molecule of cystine and a molecule of iodine or substances whose concentrations are proportional to their concentrations". Later in the same paper they discuss the possibility that triiodide is the reactant because of the small change in the rate constant when the iodide ion concentration is varied. However, in all the reactions which we have studied, the iodide dependence of the rate is interpreted in terms of iodine as the electrophilic species and not triiodide. Our data for the quaternary salt **3** and for the primary amine **4** at low pH similarly show only a small response of the rate constants to added iodide, however

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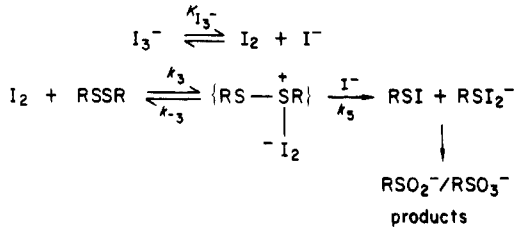
Scheme II. General Mechanism of I_2 Cleavage of Disulfides



on closer inspection we find that the rate constant $k = c([I^-] + d)^{-1}$ M^{-1} s^{-1}. This type of iodide dependence suggests that the iodine–disulfide complex is present at steady-state concentration and is cleaved by iodide ion as we proposed by path 2 in Scheme I. Since $-d[I_3^-]/dt = [RSSR{\cdot}I_2][I^-]k_5$ the steady-state approximation on RSSR·I_2 yields

$$-d[I_3^-]/dt = \{[I_2][I^-][RSSR]k_3\}/\{k_{-3}/k_5 + [I^-]\}$$

Since $[I_3^-]/\{[I_2][I^-]\} = 723$, then

$$-d[I_3^-]/dt = \{[RSSR][I_3^-]k_3\}/\{723(k_{-3}/k_5 + [I^-])\} \quad (3)$$

Values for k_{-3}/k_5 are 0.10 for the quaternary salt **3** and 2 for the primary amine **4**.

When the rate equation (eq 3) is applied to the data for cystine (ref 2, Figure 1) the equation which describes the initial rate constants is $k_2 = 0.61(0.5 + [I^-]^{-1})$. Thus, as shown in Figure 1, $k_{-3}/k_5 = 0.5$ for the reaction of the cystine according to the mechanism in Scheme II. Thus, for disulfide cleavage reactions in the absence of neighboring group participation the reaction is most probably initiated by electrophilic coordination of iodine to the disulfide, followed by nucleophilic attack of iodide at the adjacent sulfur.

This study of the effect of neighboring amines on the oxidative cleavage of disulfides by aqueous iodine has provided examples of reactions which give cyclized products and of anchimerically assisted reactions. Additionally, a general mechanism for the oxidative cleavage of disulfides in the absence of suitably placed neighboring groups has also been obtained.

Acknowledgment. We wish to thank Dr. Lawrence Coleman, Department of Physics, University of California, Davis, for the use of the Nicolet FT-IR and Edward Tang for the preparation of compound **4**. We also wish to thank Professor T. C. Bruice for a helpful discussion.

Registry No. **1**, 31060-90-9; **2**, 463-22-9; **3**, 26281-56-1; **4**·2HBr, 83626-59-9; **5**, 93531-48-7; **6**, 93531-49-8; **7**, 37441-50-2; cystine, 56-89-3.

Neighboring-Group Participation in Organic Redox Reactions. 10. The Kinetic and Mechanistic Effects of Imidazole and Benzimidazole Nitrogen on Thioether Oxidations[1]

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Received July 2, 1984

The kinetics of the aqueous iodine oxidation of a number of imidazolyl- and benzimidazolylalkyl methyl sulfides have been studied. Evidence of neighboring-group participation has been observed in all cases. The anchimeric assistance provided by the benzimidazole moiety is evidenced by rate accelerations of 10^2–10^5. The oxidation of 1-methyl-2-[3-(methylthio)propyl]imidazole, **1**, is 10^6 times faster than that of simple thioethers and is faster than any previously reported acyclic thioether. The reaction of 2-[3-(methylthio)propyl]benzimidazole is accelerated by 10^5 via a transient N–S dication. Additionally, the pH profiles of all of the compounds studied provide strong evidence for N–S interacted intermediates.

Introduction

Neighboring nucleophiles can dramatically accelerate the rate of thioether redox reactions.[2] Previous studies of thioethers containing neighboring amine groups (primary, secondary, and tertiary aliphatic amines and pyridine) revealed that amines are particularly adept at this sort of intramolecular catalysis.[3-5] Consequently, investigation of the imidazole group, which is not only a good nucleophile but biologically ubiquitous as well, seemed a logical extension of the earlier work. Previous work with other thioethers definitely indicated that the entropic advantages of a mesocyclic compound were considerable; however, the synthesis of cyclic imidazole thioethers seemed formidable. Attention was accordingly directed towards acyclic compounds (**1**–**5**).

Table I. Summary of Kinetic Data

reaction order in	1	2	3	4	5
thioether [RSR] at pH 8.0	1.2	1.1	1.0	1.0	1.0
$[I^-]$ at					
pH 8.0	−2.2	−1.7	−1.7	−1.8	−2.5
pH 7.0	*a*	*a*	*a*	−1.7	−2.5
pH 5.0	*a*	*a*	*a*	*a*	−2.6
titrimetric pK_a	7.9	6.2	6.4	6.3	6.2
kinetic pK_a	8.0	5.8	5.7	6.4	6.9
relative rate at 0.025 M KI pH 8.0	2900	2	1	300	140

[a] Not determined.

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0022-3263/85/1950-0004$01.50/0