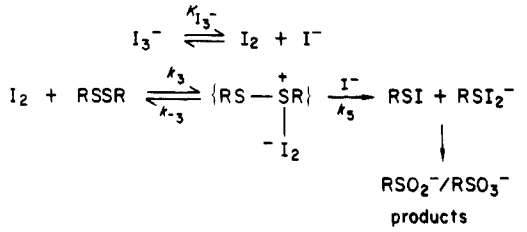
Scheme II. General Mechanism of I_2 Cleavage of Disulfides



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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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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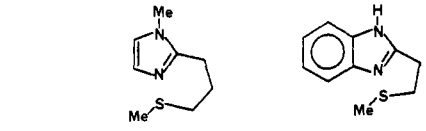
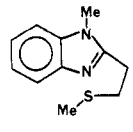
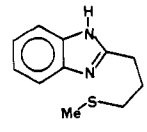


1

2



3



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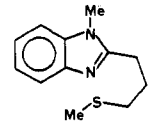

5

The effects of imidazole and benzimidazole nitrogen upon the the oxidation of thioethers **1–5** by aqueous I_2 (eq 1) was evaluated. The rate accelerations listed in Table

$$RSR + I_3^- + H_2O \rightleftharpoons R_2SO + 2H^+ + 3I^- \quad (1)$$

V range from moderate in the case of **5** to dramatic in the case of **1**. The pH profiles of the reactions of all compounds offer conclusive evidence of neighboring-group participation. The kinetic results are summarized in Table I and in Figures 1–3.

Experimental Section

Materials. The preparation of the imidazolyl and benzimidazolyl thioethers is outlined below. The structures of these and other compounds were verified by a combination of ^1H NMR (Varian EM-360, EM-390), high-resolution mass spectrometry (DuPont 492), and elemental analysis (for solids).

3-Iodopropyl Methyl Sulfide. A 200-mL flask equipped with a stir bar and a reflux condenser was charged with 3-chloropropyl methyl sulfide[6] (9.0 g, 0.072 mol), sodium iodide (13.5 g, 0.090 mol), and 75 mL of dry acetone. After 2 h stirring at room temperature no NaCl had precipitated, so heating was begun. After 21 h of refluxing the filtered solution was concentrated under reduced pressure. The yellow residue was taken up into methylene chloride, filtered, and decolorized by washing with aqueous thiosulfate solution. Filtration and concentration under reduced pressure yielded 11 g of a slighly yellow oil which upon vacuum distillation (315–317 K (0.15 torr)) provided 6.2 g (40%) of slightly yellow product. The iodide was flushed with Ar, protected from light, and stored at 258 K. NMR (CCl_4, 60 MHz) δ 3.2 (t, 2 H, CH_2I), 2.5 (m, 2 H, CH_2S), 2.1 (s, 3 H, CH_3S), 2.0 (m, 2 H, CH_2).

1-Methyl-2-[3-(methylthio)propyl]imidazole (1). A dry 100-mL three-necked flask equipped with a stir bar, spirit thermometer, and septa was charged with 50 mL of freshly distilled (from $LiAlH_4$) tetrahydrofuran and cooled to 230 K under Ar. Then dry (stored over 3 Å sieves) *N*-methylimidazole (2.16 g, 0.026 mol) followed by *n*-butyllithium (15.3 mL, 0.026 mol, 1.7 N in hexane) were added slowly by syringe so as to keep the temperature below 230 K. After 15 min, freshly prepared 3-iodopropyl methyl sulfide (6.2 g, 0.029 mol) was added via syringe over 20 min, again keeping the temperature below 230 K. The solution was then allowed to warm slowly to room temperature overnight. The solution was diluted with 50 mL of ether and extracted (4 × 25 mL) with 1 N HCl. The pH of the acidic extract was taken to pH 9 with $NaHCO_3$, extracted (4 × 50 mL) with chloroform, and dried. Concentration under reduced pressure followed by vacuum distillation (361–366 K (0.05–0.025 torr)) yielded 2.30 g (51%) of a colorless liquid which was stored under Ar at 258 K. The product was further purified by preparative GC at 375 K: NMR (CCl_4, 60 MHz) δ 6.6 (d, 2 H, ring H's), 3.55 (s, 3 H, NCH_3), 2.6 (m, 4 H, CH_2CH_2), 2.0 (m, 2 H, CH_2S), 2.0 (s, 3 H, CH_3S); MS, M^+ calcd 170.0879, found 170.0913.

Benzimidazolylalkyl Methyl Sulfides and Precursors. All of the benzimidazoles prepared were obtained by Phillips condensations between the appropriate phenylenediamine and the appropriate carboxylic acid.[7] *o*-Phenylenediamine was purchased from Aldrich Chemical Co., Inc. and used without further purification. 3-(Methylthio)propionic acid was prepared by the method of Challenger and Hollingsworth.[8] *N*-Methyl-*o*-phenylene diamine and 4-(methylthio)butyric acid were prepared as described below:

***N*-Methyl-*o*-phenylenediamine** was prepared by a modification of the method of Usherwood and Whitely.[9] The *p*-toluenesulfonanilide of *o*-nitroaniline was prepared according to the reference (73% yield). However, rather than methylating the sulfonanilide with dimethyl sulfate, methyl iodide was used to methylate the potassium salt in refluxing ethanol (100% yield). Subsequent hydrolysis of the sulfonanilide (82% yield) and reduction of the nitro group (80% yield) with tin and hydrochloric acid was accomplished as described in the reference. The yield from *o*-nitroaniline was 48%: NMR ($CDCl_3$, 90 MHz) δ 6.8 (m, 4 H, ring H's), 3.3 (broad s, 3 H, NH), 2.75 (s, 3 H, NCH_3).

4-(Methylthio)butyric Acid. Sodium methanethiolate[6] (17 g, 0.24 mol) and γ-butyrolactone (16 g, 0.18 mol) were dissolved in 150 mL of dry (stored over 3 Å sieves) Me_2SO, flushed with Ar, and stirred. After 116 h, 400 mL of 1 N HCl was added and the aqueous solution was extracted (4 × 250 mL) with ether. The dried ether solution was concentrated under reduced pressure to a constant weight of 24.2 g (98%): NMR (neat, 60 MHz) δ 10.2 (s, 1 H, COOH), 2.6 (m, 4 H, CH_2CH_2), 2.2 (s, 3 H, CH_3S), 2.0 (m, 2 H, CH_2S).

Benzimidazolylalkyl Methyl Sulfides. A solution of 0.014 mol of the appropriate carboxylic acid, 0.013 mol of the appropriate phenylenediamine, 10 mL of concentrated HCl, and 10 mL of H_2O were refluxed for 20 h. After concentration under reduced pressure the resultant sludge was dissolved in 10 mL of H_2O and the solution slowly poured into 20 mL of cold, concentrated, aqueous ammonia. The resultant precipitate was collected and purified as described below:

2-[2-(Methylthio)ethyl]benzimidazole (2). The crude product was recrystallized first from 95% ethanol then from (50/50 v/v) ethanol/water. The recrystallized material was then vacuum sublimed twice at 420 K (0.025 torr). The resulting white crystals were stored under Ar at 258 K: TLC R_f 0.39 (20% ethanol in $CHCl_3$); mp 432–437 K dec (lit.[10] mp 437–440 K; NMR ($CDCl_3$, 90 MHz) δ 7.5 (m, 4 H, ring H'S), 3.0 (m, 4 H, CH_2CH_2), 2.0 (s, 3 H, CH_3S). The imino hydrogen was not observed by NMR.[11] Anal. Calcd for $C_{10}H_{12}N_2S$: C, 62.46; H, 6.29; N, 14.57. Found: C, 62.66; H, 6.38; N, 14.61.

1-Methyl-2-[2-(methylthio)ethyl]benzimidazole (3). The crude purple crystals were recrystallized once from (50/50 v/v) ethanol/water then column chromatographed (5–10% ethanol in $CHCl_3$). The resultant beige crystals were stored under Ar at 258 K: TLC R_f 0.47 (20% ethanol in $CHCl_3$); mp 335–336 K; NMR ($CDCl_3$, 90 MHz) δ 7.7 (m, 1 H, C4-H), 7.2 (m, 3 H, C5–C7 H's), 3.7 (s, 3 H, NCH_3), 3.1 (m, 4 H, CH_2CH_2), 2.15 (s, 3 H, CH_3S). Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 63.77; H, 6.76; N, 13.63.

2-[3-(Methylthio)propyl]benzimidazole (4). The crude product was column chromatographed (5–10% ethanol in $CHCl_3$) then recrystallized from aqueous methanol by adding water to a hot concentrated methanolic solution until a slight turbidity appeared. The resultant white crystals were stored under Ar at 258 K: TLC R_f 0.52 (20% ethanol in $CHCl_3$); mp 411–412 K;

(1) For paper 9 in the series: Doi, J. T.; Musker, W. K. *J. Am. Chem. Soc.* **1984**, *106*, 1887–1888.
(2) Musker, W. K. *Acc. Chem. Res.* **1980**, *13*, 200–206.
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(10) Castle, R. N.; Gerhardt, G. A. *J. Heterocycl. Chem.* **1965**, *2*, 306–307.
(11) The NH signal of the benzimidazoles and imidazoles are typically very broad and are often obscured by baseline noise. The NH signal of the conjugate acids however, are readily observable.

Table II. Spectral Data for Sulfoxide Products

no.	IR SO stretch, cm^{-1}	NMR[a] SMe, ppm
1	1030	2.45 (2.00)
2	1025	2.70 (2.00)
3	1040	2.60 (2.15)
4	1025	2.50 (2.00)
5	1040	2.60 (2.10)

[a] Values for corresponding sulfides in parentheses.

NMR ($CDCl_3$, 90 MHz) δ 11.9 (s, 1 H, NH), 7.3 (m, 4 H, ring H's), 3.1 (t, 2 H, bz CH_2), 2.5 (m, 2 H, CH_2), 2.1 (m, 2 H, CH_2S), 2.0 (s, 3 H, CH_3S). Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 63.58; H, 6.86; N, 13.59.

1-Methyl-2-[3-(methylthio)propyl]benzimidazole (5). The crude, green colored product was recrystallized from (50/50 v/v) ethanol/water then column chromatographed (5–20% ethanol in $CHCl_3$). The chromatographed material was then recrystallized twice from absolute ethanol. The resultant beige crystals were stored under Ar at 258 K: TLC R_f 0.45 (20% ethanol in $CHCl_3$); mp 331–332 K; NMR ($CDCl_3$, 90 MHz) δ 7.7 (m, 1 H, C4-H), 7.2 (m, 3 H, C5–C7 H's), 3.7 (s, 3 H, NCH_3), 2.9 (m, 2 H, bz CH_2), 2.6 (m, 2 H, CH_2), 2.2 (m, 2 H, CH_2S), 2.1 (s, 3 H, CH_3S). Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.12; H, 7.26; N, 12.56.

Products. The oxidation products were the sulfoxides in all cases. The sulfoxide of 1 was prepared in aqueous methanol by using a previously described technique.[12] However, due to the reduced solubility of the benzimidazoles in the aqueous methanol solution, the following procedure was adopted:

A 500-mL flask was charged with 200 mL of a 1 mM solution of the appropriate thioether and 30 mg (0.30 mmol) of $KHCO_3$. Then 2.0 mL of a KI/KI_3 solution (0.20 mmol total oxidant) was added over 1–5 min. As the KI/KI_3 solution was added, a localized brownish precipitate formed (presumably the I_2 complex) which quickly dissolved yielding a yellow solution which equally quickly decolorized. After stirring overnight, the solution was dried under reduced pressure. The residue was then triturated with 2 mL of $CHCl_3$ and the $CHCl_3$ solution was evaporated to dryness under reduced pressure. The resultant residue, typically 25 mg, was then taken up into 0.5 mL of $CDCl_3$ and filtered, and the ^1H NMR and solution IR spectra were determined. The NMR spectra of the sulfoxides were essentially identical with those of the corresponding sulfides with the exception of a downfield shift of the signals from the methylene and methyl protons immediately adjacent to the sulfur. The chemical shift of the *S*-methyl signal of the sulfoxide vs. that of the corresponding sulfide as well as the infrared sulfoxide stretch are listed in Table II.

Physical Measurements. Procedures for the kinetic measurements have been described previously.[13] Oxidation rates of the thioethers were first order in I_3^- for greater than two half-lives. Ten data points, equally spaced over two half-lives, were used in determining the rate constants. Analytical reagent grade salts and acids were used to prepare the solutions. The pK_a's were determined by the method of Angelici[14] at an ionic strength of 0.25 M. All measurements were made at 299 K. The solubility of the benzimidazoles in water at the millimolar level was verified by comparison of the ultraviolet spectra of 95% aqueous methanol solutions. There were no differences between the solution prepared from aqueous stock solutions and those prepared from methanolic stock solutions.

Results and Discussion

Aqueous I_2 Oxidation of the Thioethers. As previously described,[13] the thioethers are oxidized by a limiting quantity of iodine in buffered aqueous KI solutions. The rate of oxidation is followed by monitoring the decrease in absorbance of I_3^- at 354 nm. All plots of ln *A* vs. time are linear for at least two half-lives. The pseudo-first-order rate constants, k_{obsd}, are first order in [RSR] as shown in Table I, row 1. Dividing the pseudo-first-order rate constant, k_{obsd}, obtained from eq 2, by the thioether concentration (typically 5×10^{-4} M) gives the pseudo-second-order rate constants used in Figures 1–3. As shown in Table II, the IR and ^1H NMR spectra of the oxidation products characterize these compounds as the corresponding sulfoxides.

$$d[I_3^-]/dt = -k_{obsd}[I_3^-] = -d[RSR]/dt \quad (2)$$

Table III. Summary of Buffer Effects

	percent reactn via buffer at 0.0125 M				
pH	1	2	3	4	5
		Phosphate			
8.0	0	29	22	7	46
7.0	0	25	7	0	48
6.0	0	9	5	0	35
		Cacodylate			
6.2	*a*	*a*	*a*	17	*a*
5.2	*a*	*a*	*a*	0	*a*
		Acetate			
5.5	*a*	*a*	*a*	22	*a*
5.0	0	0	0	30	22
4.0	0	0	0	0	0

[a] Not determined.

Compounds **1–4** will be discussed first because they had similar kinetic behavior, in marked contrast to that of compound **5**.

For compounds **1–4** the rate of oxidation was approximately inversely proportional to the square of the iodide concentration (Table I, rows 2–5). A 10-fold range of iodide concentration was used in each case; chosen from a larger range of 0.250–0.0025 M depending upon the rate of the oxidation. Similar minor deviations from the integral value of inverse second have been reported previously.[15]

A series of buffers were employed to maintain the pH of each run at the desired value. Acetate buffer was employed at pH 4.0 and 5.0; phosphate at pH 6.0, 7.0, and 8.0; and borate buffer at pH 9.5. In addition, for as yet undetermined reasons, acetate buffer gave inconsistent results with compound **4**; consequently, cacodylate buffer was used instead (at pH 5.2 and 6.2). For the bulk of the determinations, the buffer concentrations were 0.0125 M. No buffer dependence (a change in the observed rate upon changing the buffer concentration) was observed for compound **1**. With phosphate at pH 8.0 compounds **2–4**, however, all exhibited a buffer dependence which predictably trailed off in going to lower pH (7.0 and 6.0). A slight buffer dependence was observed for compound **4** with cacodylate buffer at pH 6.2 but not at pH 5.2. All of the buffer dependences observed were linear and in no case were they complete; that is, there was always a buffer independent path (which, in fact, predominated). The percent of each oxidation occurring via the buffer dependent path for the various compounds and buffers is tabulated in Table III.

In each case as shown in Table I, row 1, the rate of oxidation was directly proportional to the thioether concentration over a 2-fold concentration range. Use of a larger range was precluded by the desire to maintain pseudo-first-order conditions by using a large excess of thioether on the one hand and by the limited solubility

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(15) Doi, J. T.; Musker, W. K.; deLeeuw, D. L.; Hirschon, A. S. *J. Org. Chem.* **1981**, *46*, 1239–1243.

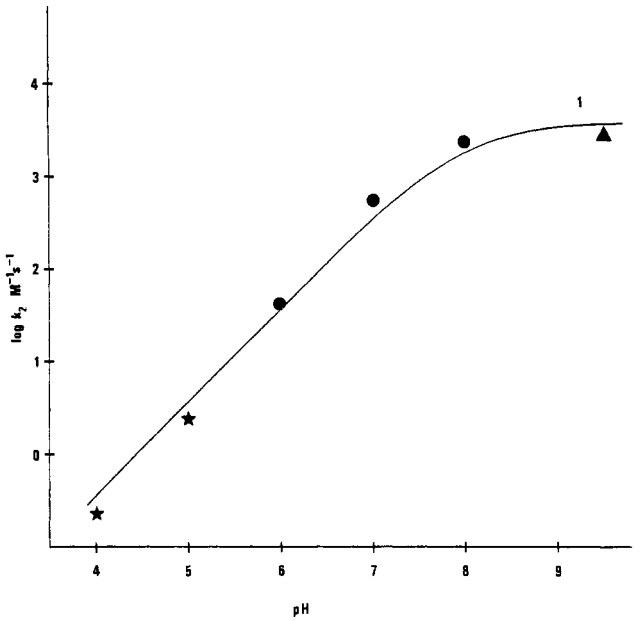


Figure 1. Effect of pH on the rates of oxidation of 1 (0.0250 M KI): (▲) 0.0125 M borate, (●) 0.0125 M phosphate, (★) 0.0125 M acetate.

of the thioethers on the other.

The pH dependence of the compounds is complicated by the presence of the basic neighboring group. A discussion of the particulars for compound 1 is illustrative. The pH dependence of the oxidation of 1 (at 0.025 M KI) was decidedly, though not surprisingly, nonlinear. A plot of pH vs. log k_{obsd} is shown in Figure 1. Similar behavior has been observed previously in the case of other amine thioethers.[15] The observed curvature can be readily explained by the change in the amount of the free base relative to its conjugate acid. In the pH range where the imidazole is substantially protonated, each successive increase of one pH unit corresponds to a 10-fold increase in the concentration of the free base and in accordance with the observed first-order sulfide dependence, the slope of the plot in this region should be one. As the pH approaches a value equal to the pK_a, the slope levels off. At successively higher pH's the concentration of the free base effectively stops changing and consequently the slope asymptotically approaches a line with a slope of zero.

The pK_a of the responsible species, the kinetic pK_a, can be determined from the data by a variety of curve fitting techniques. If the only relevant factor that changes with pH is the fraction of free base (the effective concentration of sulfide—denoted as [RSR]*), then dividing the observed pseudo-first-order rate constant by [RSR]* should yield a new constant having dimensions M^{-1} s^{-1} (eq 3).

$$k_{obsd}/[RSR]^* = \text{constant} \quad (3)$$

By varying the pK_a and minimizing the standard deviation of the resultant constants, the best fit pK_a value may be obtained. The pK_a value (to the nearest 0.1 pK_a unit) determined by this technique was 8.0 for compound 1. The titrimetrically determined pK_a of 1 was 7.9 (Table I, rows 4 and 5). The curve in Figure 1 was generated by using the kinetically determined pK_a and the average value of the second-order constants. Similar results were obtained for compounds 2–4 as shown in Figures 2 and 3. In those cases where a buffer dependence was observed the rate data were extrapolated to zero buffer concentration.

Finally, the ionic strength of the solutions was maintained at approximately 0.25 M by the addition of KCl such that variations were less than 10%. No significant change in oxidation rate was observed even when the ionic strength was doubled.

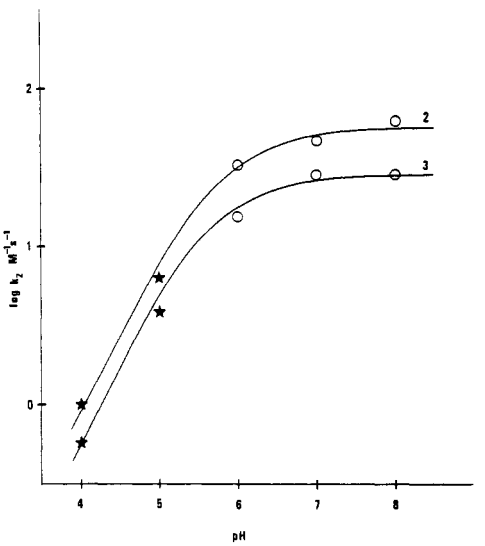


Figure 2. Effect of pH on the rates of oxidation of 2 and 3 (0.00625 M KI): (○) phosphate extrapolated to zero molar, (★) 0.0125 M acetate.

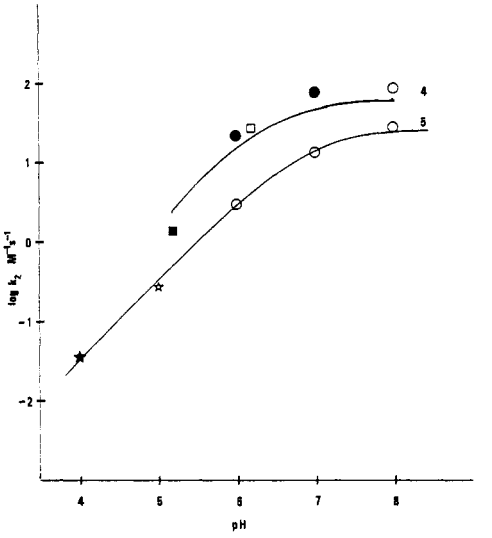


Figure 3. Effect of pH on the rates of oxidation of 4 and 5 (0.0625 M KI): (○) phosphate extrapolated to zero molar, (●) 0.0125 M phosphate, (□) cacodylate extrapolated to zero molar, (■) 0.0125 M cacodylate, (☆) acetate extrapolated to zero molar, (★) 0.0125 M acetate.

Combining the above data results in the generalized rate law for compounds 1–4, where $k_2 = 0$ for compound 1.

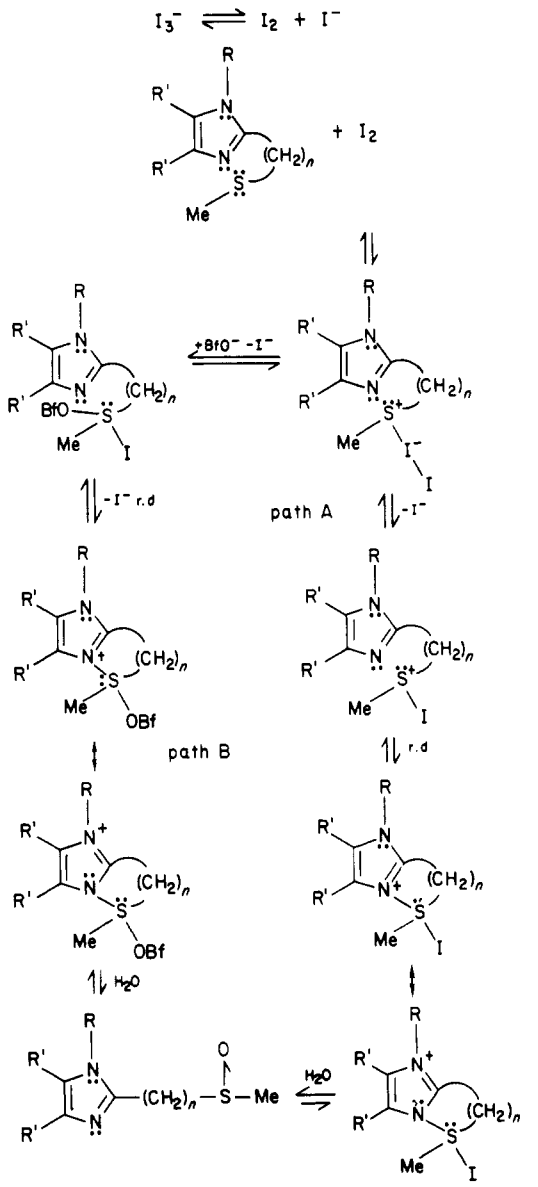
$$-d[I_3^-]/dt = k_1[RSR]^*/[I^-]^2 + k_2[RSR]^*[buffer]/[I^-]^2$$

A mechanism consistent with the observed rate data for compounds 1–4 is shown in Scheme I. The initial step is the dissociation of triiodide into iodine and iodide (K for formation = 723 at 298 K[16]) providing the first inverse iodide. This is followed by iodine attack to form the iodine complex.[17] At this point, two paths, A and B, must be formulated to account for the observed buffer dependences. In path A, loss of iodide from the iodine complex

(16) Daniele, G. *Gazz. Chim. Ital.* **1960**, *90*, 1068–1081.

(17) The iodine complex can be seen forming during the product runs as a brown precipitate. A crystal structure of the diiodine complex of 1,5-dithiacyclooctane has been determined. Nichols, B. G. Ph.D. Thesis, University of California—Davis, 1981.

Scheme I. Generalized Mechanism for the Aqueous Iodine Oxidation of 1-4[a]



[a] R = hydrogen or methyl; R' = hydrogen or benz-; n = 2 or 3.

provides the second inverse iodide term and results in the formation of an iodosulfonium ion. Then in the rate-determining step, participation by the neighboring imidazole occurs. Whether this occurs via a stepwise process as indicated or by a concerted S_N2 process with concomitant loss of the third iodide can not be determined by the available kinetic data. There is no doubt however, that the third iodide is lost after the rate-determining step as no evidence for an inverse third-order path with respect to iodide was observed for compounds 1–4. Recent reports have shown that hypervalent sulfur species can be stabilized both by the use of axially oriented electronegative substituents and by incorporation into cyclic systems.[18,19] Thus the iodosulfurane structure postulated seems likely. Note that participation of the neighboring imidazole to yield a cyclic iodosulfurane allows the positive charge to be delocalized.

(18) Martin, J. C.; Perozzi, E. F. *Science (Washington, D.C.)* **1976**, *191*, 154–159.
(19) Adzima, L. J.; Chiang, C. C.; Paul, I. C.; Martin, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 953–962.

In path B on the other hand, attack of buffer (represented generically as BfO^-) and loss of the second iodide must result in a sulfurane species since there is again no evidence of an inverse third-order path in iodide. Attack by the neighboring imidazole follows, again resulting in a resonance stabilized sulfurane which, as before, is ultimately hydrolyzed to the product sulfoxide. No evidence was obtained to indicate that hydrogen ion is lost from the sulfurane intermediates formed from compounds 4 and 2 to form a neutral sulfurane species. This may indeed happen but the lifetime of such a species in the aqueous media employed would be exceedingly brief.

In each case, neighboring-group participation occurs after a positive charge has formed upon the sulfur, and the basicity of the resultant charged species might well be expected to differ from that of the parent compound. The data in Table I show that this is indeed the case for compounds 2 and 3 where the positive charge is only two methylene units removed from the basic pyridine-like nitrogen. In compounds 1 and 4 there are three intervening methylene units and the kinetic and titrimetric pK_a's are essentially the same.

The oxidation kinetics of 5, while notably different from those of 1–4, did exhibit some similar features. The rate of oxidation was directly proportional to the concentration of thioether, as expected. Linear buffer dependences were observed with phosphate at pH's 8.0, 7.0, and 6.0. The results tabulated in Table III show that the fraction of the oxidation occurring via the buffer pathway does not fall in going from pH 8.0 to 6.0 as rapidly as does the concentration of the dibasic HPO_4^{2-} ion. This indicates that the less nucleophilic $H_2PO_4^-$ is participating as well, although the data obtained did not provide consonant values for the fractions of the buffer pathway due to each of the phosphate ions. Somewhat surprisingly, a small buffer dependence was observed with the weakly nucleophilic acetate at pH 5.0 which accounted for 22% of the reaction at a 0.0125 M acetate concentration. The pH profile of 5 was similar to that of 1–4. Figure 3 shows a plot of pH vs. the log of the extrapolated (to zero buffer) rate constant. The best-fit "kinetic" pK_a (determined as before) was 6.9 vs. a titrimetric pK_a of 6.2. One notable difference however, is that the kinetic pK_a of 6.9 is higher than the titrimetric pK_a of 6.2. As before, doubling the ionic strength had no significant effect upon the oxidation rate.

The observed iodide dependences (all at 0.0125 M buffer) are shown in Table I. Unlike those for compounds 1–4, the iodide dependence for 5 was not simple. The apparent nonintegral order resulted from plots of ln k_{obsd} vs. ln $[I^-]$ which tend toward a slope of −2 at the higher iodide concentrations and toward a slope of −3 at lower concentrations, which is indicative of two parallel paths. If the observed orders in iodide are the result of parallel inverse third and inverse second paths, then the following relationships can be derived:

$$k_{obsd} = k_1[I^-]^{-2} + k_2[I^-]^{-3}$$

$$k_{obsd}[I^-]^2 = k_1 + k_2[I^-]^{-1}$$

A plot of $k_{obsd}[I^-]^2$ vs. $1/[I^-]$ should then be linear. This was true for each of the pH's (8.0, 7.0, and 5.0) at which the iodide dependence was determined. A plot of $k_{obsd}[I^-]^2$ vs. $1/[I^-]$ at pH 8.0 is shown in Figure 4.

The question remains as to whether the buffer dependent paths are associated with either the inverse second-order or the inverse third-order path in iodide. The percentages of the reaction occurring via the various paths ([buffer] = 0.0125 M) are listed in Table IV. Obviously, the buffer dependent path(s) and the inverse second-order

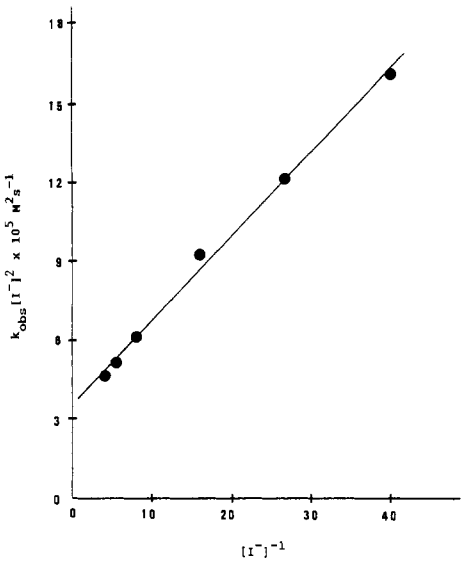


Figure 4. Plot of $k_{obsd}[I^-]^2$ vs. $[I^-]^{-1}$ at pH 8.0 for **5**; $k_{obsd}[I^-]^2 = 3.6 \times 10^{-5} + 3.2 \times 10^{-6}[I^-]^{-1}$.

Table IV. Observed Percentages of I_2 Oxidation of 5 Occurring via Buffer Dependent and $[I^-]^{-2}$ Paths

	percent reaction via		
pH	species	$[buffer]_{tot}$	$[I^-]^{-2}$
8.0	phosphate	46	42
7.0	phosphate	48	44
6.0	phosphate	35	
5.0	acetate	22	31
4.0	acetate	00	

path in iodide are one in the same.

Combining the above data results in the rate law:

$$-d[I_3^-]/dt = k_2[RSR]^*[buffer]/[I^-]^2 + k_3[RSR]^*/[I^-]^3$$

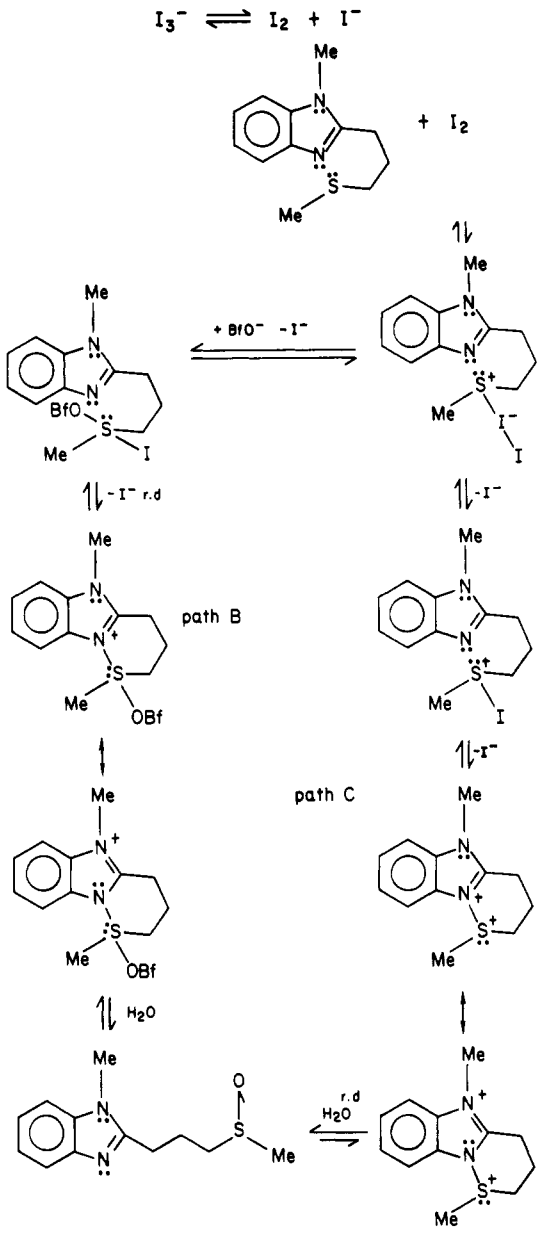
A mechanism consistent with this rate law is shown in Scheme II. As before, the initial steps involve the dissociation of triiodide followed by attack of iodine to form the iodine complex. At this point two paths (B and C) must be formulated to account for the observed buffer dependences and the nonintegral iodide dependence. Path B, the buffer dependent path, is identical with path B for compounds 1–4 of Scheme I. In path B the third iodide is lost after the rate-determining step. In path C however, neighboring-group participation by the imidazole is followed by loss of the third iodide **prior** to the rate-determining step. Again, this may occur either by a stepwise process with an intermediate iodosulfurane or by a concerted S_N2 process. In any event, the third iodide is lost with the resultant formation of a resonance stabilized dication as shown. Similar N–S bonded (and in the case of 1,5-dithiacyclooctane, S–S bonded) dicationic species have been characterized previously.[3] Subsequent hydrolysis of the resonance stabilized sulfurane of path B and the dication of path C yields the sulfoxide product.

Trends in Imidazole (Benzimidazole) Thioether Oxidations. There are three major structural features that were varied in the above study: (1) benzimidazole vs. imidazole nuclei; (2) interaction via a five- or six-membered ring (N-5 vs. N-6 participation); (3) hydrogen vs. methyl substitution on the imino nitrogen.

The relative effect of these three factors upon the rate of oxidation was ring size > nucleus > N substitution.

The most favorable ring size for interaction is a function of two major parameters. Entropy favors the formation of smaller rings over larger ones and if this was the only (or the dominant) factor then the preferred order of ring

Scheme II. Generalized Mechanism for the Aqueous Iodine Oxidation of 5



sizes would simply be 3 > 4 > 5 > 6... and so on. Enthalpy, in the form of ring strain, must also be considered though, and it frequently results in a substantial reordering of the above sequence.

The similarity in the preference for interaction via five- and six-membered rings in so many systems results in a particular sensitivity to relatively minor changes in the geometries of the reactants. For many aliphatic, acyclic systems, participation via five-membered rings typically provides about a 10- to 50-fold rate enhancement over the corresponding six-membered ring case.[20] This is primarily due to the entropic advantages which more than offset the relatively minor enthalpic disadvantages.

In the present case however, when the reactivity of **4** is compared to **2** and **5** to **3**, the rate of reaction via N-6 is ~150 times faster than via N-5. The rigidity of the imidazole moiety reduces the entropic disadvantages for both

(20) (a) Capon, B.; McManus, S. P. "Neighboring Group Participation"; Plenum Press: New York, 1976; Vol. 1, Chapter 2, pp 43–53 and references cited therein. (b) The rate of iodine oxidation of 3-aminopropyl methyl sulfide is ~50 times faster than the oxidation rate of 4-aminobutyl methyl sulfide. deLeeuw, D. L., unpublished results.

Table V. Normalized Relative Rates at pH 8.0, 0.0250 M KI

1-thia-5-oxacyclooctane (5-oxathiocane)[22]	1
1-thia-6-oxacyclodecane (6-oxathiotane)[22]	3
thiacyclooctane (thiocane)[13]	40
1-methyl-2-[2-(methylthio)ethyl]benzimidazole, 3	700
2-[2-(methylthio)ethyl]benzimidazole, 2	1600
2-[2-(methylthio)ethyl]pyridine[15]	1600
1-methyl-2-[3-(methylthio)propyl]benzimidazole, 5	100000
2-[3-(methylthio)propyl]benzimidazole, 4	200000
1-methyl-2-[3-(methylthio)propyl]imidazole, 1	2000000

N-5 and N-6 participation from what it would be in the analogous acyclic cases. Additionally, the geometry of the imidazole ring is such that N-5 participation produces a considerably more strained intermediate than N-6 participation, primarily as a result of the rigid angular constraint of the sp^2 hybridized atoms. Similar results have been reported when unsaturation is introduced into the system.[20a] Knowledge of $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ for the cyclization step would be illuminating; however, only the overall, composite values (which include the preequilibria as well) can be determined.

The rate acceleration observed upon changing from a benzimidazole nucleus to an imidazole nucleus is to be expected. Inductive electron withdrawal by the benzene ring is the primary cause of the greater nucleophilicity of imidazole relative to benzimidazole.[21] The difference in this case (a factor of 20—see Table V) is not great and is smaller at lower iodide concentrations. In light of the difference in mechanism, not too much significance should be attributed to it. Additionally, solvation effects undoubtedly play a role since 1 is highly water soluble while 5 is only slightly soluble.

In a similar fashion (comparing 5 with 4 and 3 with 2), the small increase (~2-fold) observed upon changing the substitution at the imino nitrogen from methyl to hydrogen is likely due to differences in solvation and is not particularly significant. The presence of the imino hydrogen provides the opportunity for hydrogen bonding that is not otherwise available.

Relative Rate Summary. In Table V is a listing of the relative oxidation rates for a number of thioethers studied in this laboratory. Each of these compounds has essentially an inverse second-order dependence in iodide, with the −3 order for the buffer independent path in the oxidation of 5 being the most notable deviant.

The rates have been normalized to pH 8.0 at an iodide concentration of 0.0250 M. The rates are extrapolated to zero buffer where appropriate. Finally, the relative concentrations have been adjusted in accordance with the observed pK_a and the pH where appropriate.

The cyclic ether thioethers[22] are obviously the most sluggish of the lot. The rate differences between the ether thioethers and thiocane (thiacyclooctane) border on the insignificant. The anchimeric assistance provided by the benzimidazole and imidazole groups, however, ranges from moderate (in the case of N-5 participation in the benzimidazoles) to quite dramatic in the case of N-6 participation. Clearly neighboring-group participation by imidazole (via histidine residues) has the potential for catalyzing similar redox processes in biological systems.

Acknowledgment. This research was supported by The National Science Foundation and The National Institutes of Health.

Registry No. 1, 93530-04-2; 1 (sulfoxide), 93530-10-0; 2, 4198-64-5; 2 (sulfoxide), 93530-11-1; 3, 93530-05-3; 3 (sulfoxide), 93530-12-2; 4, 93530-06-4; 4 (sulfoxide), 93530-13-3; 5, 93530-07-5; 5 (sulfoxide), 93530-14-4; 3-chloropropyl methyl sulfide, 13012-59-4; 3-iodopropyl methyl sulfide, 93530-08-6; *N*-methylimidazole, 616-47-7; *N*-methyl-*o*-phenylenediamine, 4760-34-3; 3-(methylthio)propionic acid, 646-01-5; 4-(methylthio)butyric acid, 32391-97-2; *o*-phenylenediamine, 95-54-5; potassium *o*-nitroaniline *p*-toluenesulfonanilide, 93530-09-7; *N*-methyl-*o*-nitroaniline *p*-toluenesulfonanilide, 6892-25-7; sodium methanethiolate, 5188-07-8; γ-butyrolactone, 96-48-0.

(21) Preston, P. N. "Benzimidazoles"; Weissberger, A., Taylor, E. C., Eds.; John Wiley & Sons, Inc.: New York, 1981; Vol. 40, Part 1, pp 83–148.

(22) 5-Oxa-1-thiacyclooctane was prepared by cyclizing bis(4-bromopropyl) ether by an adaptation of the method of Singh, A.; Mehrotra, A.; Regen, S. L. *Synth. Commun.* **1981**, *11*, 409–411. The dichloro ether was prepared by the method of Sieber, G.; Ulbricht, I. *J. Prakt. Chem.* **1963**, *20*, 14–19. An improved procedure (50% vs. 10% yield) for the ten-membered ring, 6-oxa-1-thiacyclodecane, was realized by cyclizing bis-(4-iodobutyl) ether by a high-dilution adaptation of the method of Hammerschmidt, W.; Bieber, W.; Vögtle, F. *Chem. Ber.* **1978**, *111*, 2445–2447. The diiodide was obtained from the dichloride via a Finkelstein reaction. The dichloride was prepared by the method of Alexander, K.; Schniepp, L. E. *J. Am. Chem. Soc.* **1948**, *70*, 1839–1842.

Manganese(III)-Mediated γ-Lactone Annulation

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The annulation of a γ-lactone ring onto an alkene by manganese(III) acetate oxidation of acetic acid was investigated. The regioselectivity of addition to unsymmetrically substituted alkenes is reported along with the stereoselectivity of addition to various acyclic and cyclic alkenes. Alkenes with ionization potentials above 8.2 eV were found to react in good yield. The role of acetic anhydride in these reactions was studied, and it was shown to be oxidized faster than acetic acid and also led to different products. The fate of oxidized acetic acid or anhydride in the absence of a suitable acceptor molecule has also been quantitatively identified. The relationship of enolizability, or C–H acidity, of the carboxylic acid being oxidized was established quantitatively.

Highly oxidized transition metals have long been used in organic synthesis (i.e., Cr(VI) in $H_2Cr_2O_7$ and Mn(VII) in $KMnO_4$) and their synthetic and mechanistic chemistry has been thoroughly studied.[1] Even so new uses are being discovered every year for these standard reagents.[2] Milder transition metal oxidants (i.e., Mn(III) species) have been far less commonly employed by synthetic chemists. Thus we have begun a program to exploit the synthetic potential

(1) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: Menlo Park, CA, 1972; pp 257–291.

(2) Lee, D. G.; Noureldin, N. A. *J. Am. Chem. Soc.* **1983**, *105*, 3188–3191.

0022-3263/85/1950-0010$01.50/0