13

orientations of orbitals 1, 11, and 10 has not been investigated.

Although the above discussion has centered on through-bond interaction of the lone-pair orbitals with each other, direct, through-space overlap of these orbitals may occur. Clearly, the overlap is a maximum when the lone-pair orbitals are collinear, as is nearly the case in Cu₂bpim³⁺, and decreasing ϕ will decrease $|J|$. It is therefore difficult to distinguish between a through-space

or through-bond mechanism for the ϕ dependence of $|J|$. Calculations show,[51] however, that the contribution from direct overlap is much smaller than that due to the indirect overlap.

Neighboring Group Participation in Organic Redox Reactions. 5.[1] The Directive and Kinetic Effects of Hydroxyl Groups on Thioether Oxidation

Albert S. Hirschon, Joyce Takahashi Doi,* and W. Kenneth Musker*

Contribution from the Department of Chemistry, University of California, Davis, California 95616. Received March 30, 1981

Abstract: Transannular interaction of the hydroxyl group during the aqueous I₂ oxidation of 5-hydroxythiacyclooctane, **2**, 4-hydroxythiacyclohexane, **4**, and 4-hydroxy-4-methylthiacyclohexane, **5**, is indicated by anchimeric assistance, by stereoselection of the trans alcohol–sulfoxide products and by the isolation of the bridged intermediate, 9-oxa-1-thioniabicyclo[3.3.1]nonane triiodide (**1**). In contrast to the behavior of amine thioethers, these reactions are more susceptible to buffer mediation. The two-term rate law indicates that there are two major pathways. Both involve hydroxyl participation and sulfurane intermediates, but one path most likely involves coordination of buffer to sulfur.

Our recent studies of intramolecular catalysis of organic redox reactions revealed that transannular thioether and tertiary amine groups cause dramatic accelerations of the rate of oxidation of thioethers by aqueous I₂.[1,2] A natural extension is the examination of the weakly nucleophilic hydroxyl group and its influence on the reaction mechanism.[3]

Studies of the mechanism of the I₂ oxidation of thioethers in aqueous solution were initiated by Higuchi and Gensch.[4,5] Their method is to monitor the decrease in the I₃⁻ concentration by its absorption at 353 nm as the reaction proceeds. Additional information about the reaction can be obtained from the retardation of the rate due to iodide inhibition. This information has been used to determine the minimum number of intermediates which must contain iodine atoms prior to the rate-determining step. Structures of many of these and other intermediates have been proposed without adequate characterization. In this study of hydroxyl group participation in the I₂ oxidation of cyclic thioethers we have isolated and determined the structure of an alkoxysulfonium salt intermediate[3] and have confirmed the stereochemistry of the products.

The alkoxysulfonium salt intermediate, 9-oxa-1-thioniabicyclo[3.3.1]nonane triiodide, is the first alkoxysulfonium salt whose crystal structure had been determined. The structures of the sulfoxide products of the reaction buffered at pH 8 or 9 were

determined both by independent syntheses and by NMR. These cyclic alcohol–sulfoxides are predominantly (>92%) the isomer in which the hydroxyl and sulfoxide groups are trans.

Since our major interest is in neighboring group participation in the I₂ oxidation of thioethers, the reactions were run under conditions in which buffer involvement would be minimized. Nevertheless, we obtained evidence for a mechanism involving two major paths: one path is buffer dependent and the other path buffer independent. These two paths were then correlated with the iodide dependence. The buffer independent path was found to be inverse first order in iodide: The major buffer dependent path is inverse second order in iodide.

From both kinetic and structural studies we have shown that hydroxyl participation does occur and the intramolecular interaction is manifested in both the kinetics and product stereochemistry. From these results a more definitive mechanism of the I₂ oxidation can be proposed which proceeds via hydroxyl-bridged sulfurane intermediates.

Experimental Section

Kinetic Measurements. Procedures have been described previously.[1,3–5] The absorbance of I₃⁻ at 353 nm followed the rate law d[I₃⁻]/d*t* = −[I₃⁻][R₂S]*k₂*. Values of *k₂* in M⁻¹ s⁻¹ are used in the figures and table. For the slower rates of **3** and of **4** in phosphate buffer, corrections were applied to the absorbances due to a very slow rate of I₃⁻ loss which was monitored in solutions in the absence of the thioether. Solutions of **2** in water were prepared immediately before they were used at pH 6 or 7. At pH 8 and 9, buffered solutions of **2** were prepared.

Materials. 5-Hydroxythiacyclooctane, **2**,[6] thiacyclooctane, **3**,[7] 4-hydroxythiacyclohexane, **4**,[8] 4-hydroxy-4-methylthiacyclohexane, **5**,[9] were

(1) For paper IV in this series, see Doi, J. T.; Musker, W. K. *J. Am. Chem. Soc.* **1981**, *103*, 1159.

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

(3) Hirschon, A. S.; Beller, J. D.; Olmstead, M. M.; Doi, J. T.; Musker, W. K.; *Tetrahedron Lett.* **1981**, *22*, 1195.
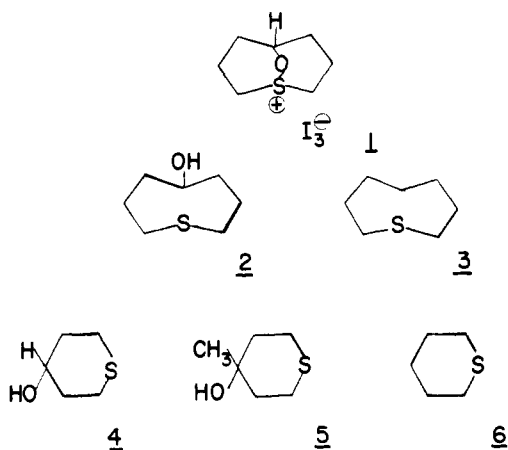
(4) Gensch, K. H.; Higuchi, T. *J. Pharm. Sci.* **1967**, *56*, 177.

(5) (a) Higuchi, T. and Gensch, K.-H. *J. Am. Chem. Soc.* **1966**, *88*, 5486. (b) Gensch, K.-H.; Pitman, I. H.; Higuchi, T. *J. Am. Chem. Soc.* **1968**, *90*, 2096.

(6) 5-Hydroxy-1-thiacyclooctane was obtained by sodium borohydride reduction of 1-thiacyclooctan-5-one in ethanol, using aqueous KOH in the workup.[2]

(7) Mandolini, L.; Vontor, T. *Synth. Commun.* **1979**, *9*, 857.

prepared by the literature references indicated. Thiacyclohexane, 6, was purchased from Aldrich and was redistilled before use. The structures of these and new compounds were checked by ^{1}H NMR (Varian EM-360, EM-390) and infrared (Perkin-Elmer 237B) spectroscopy. [13]C were determined by using a Nicolet Intermediate Field 200-MHz NMR spectrometer.

Products. The alkoxysulfonium salt was isolated during the I_2 oxidation of 5-hydroxythiacyclooctane, 2, at pH 7[2] *trans*-5-Hydroxy-thiacyclooctane 1-oxide was formed when the pH of the buffer was 9.0. The 4-hydroxythiacyclohexane 1-oxides were formed at pH 7 or 8.

When the desired products were the hydroxycycloalkane sulfoxides, the following procedure was used: 1 mmol of thioether was dissolved in 4 mL of a 50% aqueous methanol solution, 0.8 M in phosphate buffer. A solution of I_2 in methanol (2.5 mL, 0.1 g/mL) was added dropwise over several hours. The mixture was left overnight or longer. The solution was then decolorized[2] with thiosulfate, and the solvent was removed by using the rotary evaporator and by freeze-drying on the vacuum line. The residue was either triturated with $CHCl_3$ or extracted by using a Soxhlet extractor. If TLC indicated traces of starting thioether the organic product was chromatographed by using 3 g of silica gel and 5% EtOH in $CHCl_3$ as eluent. Following the elution of products an additional 50 mL of eluent was collected and tested for the presence of sulfoxides.

Products were identified as follows. *trans*-4-Hydroxythiacyclohexane 1-oxide: mp 157-158 °C (lit.[8] 159-161°); IR and ^{1}H NMR spectra are consistent with literature values; ^{13}C NMR δ ($CDCl_3$) 63.6 (C(4)), 41.2 (C(2)), 23.5 (C(3)). The same product was isolated when the pH of the reaction mixture was maintained at pH 8 by using borate buffer and adding 1 M KOH dropwise as necessary.

trans-4-Hydroxy-4-methylthiacyclohexane 1-oxide: mp 151-152 °C; ^{1}H NMR: ($CDCl_3$) δ 2.8 (m, 4), 2.15-2.65 (m, 2), 1.7 (m, 2), 1.55 (m, 1), 1.35 (s, 3); ^{13}C NMR δ ($CDCl_3$) 66.8 (C(4)), 41.6 (C(2)), 31.5 (CH_3), 27.9 (C(3)). Anal. Calcd for $C_6H_{12}O_2S$: C, 48.6; H, 8.16. Found: C, 48.1; H, 8.20.

trans-5-Hydroxythiacyclooctane 1-oxide: IR 3100-3650 (OH, br), 1015 cm^{-1} (S-O, s); ^{1}H NMR ($CDCl_3$) δ 3.8 (br, 1), 3.0 (br, 4), 1.7-2.3 (br, 9); ^{13}C NMR δ 70.1 (C(5)), 53.2 (C(2)), 33.3 (C(4)), 16.26 (C(3)).

Mixture of *cis*- and *trans*-5-Hydroxythiacyclooctane. Thiacyclooctan-5-one was treated with $NaIO_4$ to form the sulfoxide using the method of Leonard and Johnson.[10] The sulfoxide was reduced with $NaBH_4$ in ethanol and worked up with aqueous KOH to a mixture of cis and trans sulfoxides. The ^{1}H NMR was similar to that of the pure trans sulfoxide and the IR differed in the position and shape of the S-O absorbance: IR 3100-3650 (OH, br), 1020 cm^{-1} (S-O, br). The ^{13}C NMR showed two major sets of ^{13}C resonances, one set of which is identical with the set displayed by the trans isomer listed above. A third set of resonances are of lower intensity and may be attributed to the hydrogen-bonded conformation of the cis isomer. ^{13}C NMR of the cis isomer: major set, δ 69.5, 53.2, 33.6, 17.5; minor set, δ 68.9, 54.6, 33.5, 18.0. (At lower temperature the resonances of the trans isomer remained unchanged whereas the two sets of resonances for the cis isomer appeared to undergo a minor change in relative intensity or in chemical shift).

Results

Products. The final products of the oxidation of the alcohol thioethers in buffered solutions were the corresponding alcohol

(8) Klein, J.; Stollar, H. *Tetrahedron* **1974**, *30*, 2541.
(9) Borsdorf, R.; Freytag, H.; Remane, H. *J. Prakt. Chem.* **1972**, *314*, 296.
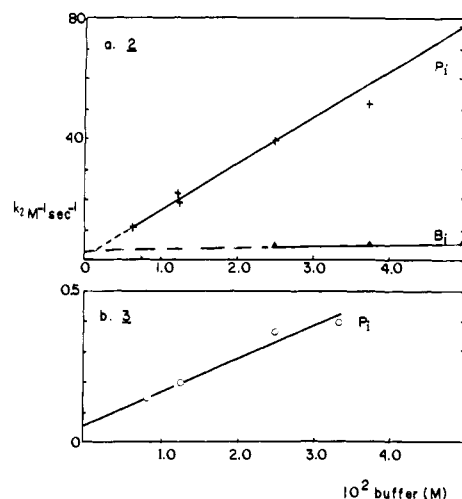(10) Leonard, N. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1962**, *84*, 3701.

Figure 1. Plots of second-order rate constants of aqueous I_2 oxidation of thiacyclooctanes vs. buffer concentration (pH 8.0; 0.030 M KI, 0.030 M KCl; [R_2S] = (40-100) × 10^{-5} M; [I_3^-]$_0$ = (2-4) × 10^{-5} M; 26.0 °C): (a) +, 2, phosphate buffer, P_i; ▲, 2, borate, B_i; (b) O, 3, phosphate, P_i.
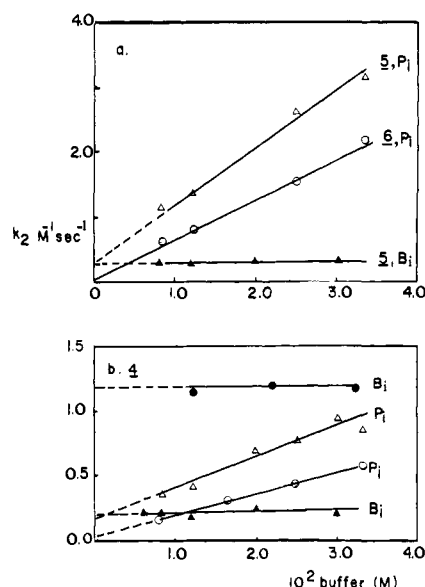

Figure 2. Plots of second-order rate constants aqueous I_2 oxidation of thiacyclohexanes vs. buffer concentration (0.030 M, KI, 0.030 M KCl; [R_2S] = (40-100) × 10^{-5} M; [I_3^-]$_0$ = (2-4) × 10^{-5} M; 26.0 °C): (a) O, 6, pH 8.0, phosphate buffer (P_i); ▲, 5, pH 8.0, borate buffer (B_i); △, 5, pH 8.0, phosphate buffer (P_i); (b) ●, 4, pH 9.0, borate buffer (B_i); △, 4, pH 8.0, borate buffer (B_i); △, 4, pH 8.0, phosphate buffer (P_i).

sulfoxides. Pure *trans*-5-hydroxythiacyclooctane 1-oxide was obtained from 2 and identified by comparison with a mixture of cis and trans products using ^{13}C NMR and IR spectroscopy. The 4-hydroxy-1-thiacyclohexane 1-oxide, obtained from the aqueous I_2 oxidation of 4, contained at least 95% of the trans isomer as determined by ^{1}H NMR and melting point. The C4 hydrogen in the trans isomer has δ 4.0 whereas in the cis isomer, δ 3.7.[8] *trans*-4-Hydroxy-4-methyl-1-thiacyclohexane 1-oxide was obtained from the I_2 oxidation of 5.

For purposes of identification, 5 was also oxidized by *m*-chloroperbenzoic acid[11] to a mixture containing trans and cis sulfoxides in the ratio of 7:3. The two sulfoxides are distinguishable by their CH_3 absorbances in ^{13}C NMR: δ 31.5 in the trans and 29.1 in the cis.[12] In the trans isomer both the OH and the S-O groups are axial;[13] the CH_3 group is equatorial. In the

(11) Johnson, C. R.; McCants, D. *J. Am. Chem. Soc.* **1965**, *87*, 1109.
(12) Gaudemer, A.; Kagan, H. B. "Stereochemistry"; Georg Thieme Verlag: Stuttgart, 1977; Vol. 1, p 106.
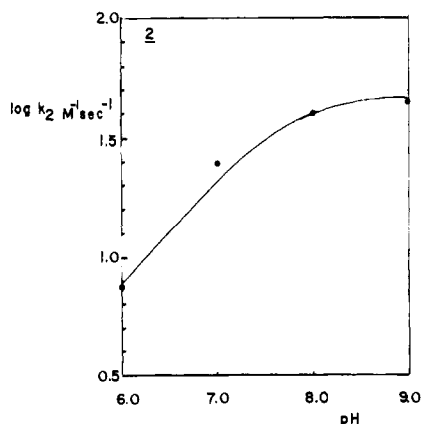
Effects of Hydroxyl Groups on Thioether Oxidation

J. Am. Chem. Soc., Vol. 104, No. 3, 1982 727

Figure 3. Plot of log k_{obsd} vs. pH for **2** (0.0250 M phosphate buffer, P_i; 0.030 M KI, 0.030 M KCl; $[R_2S] = (40-100) \times 10^{-5}$ M; $[I_3^-]_0 = (2-4) \times 10^{-5}$ M; 26.0 °C). The theoretical curve is $k_{obsd} = 5.0 + 1740[HPO_4^{2-}]$ M^{-1} s^{-1}.

Table I. Apparent Iodide Dependence of the Rate of the Oxidation of Thioethers with Aqueous Iodine (26.0 °C)

a. Thiacyclooctanes

| | | $-\Delta \log k_2/\Delta \log [I^-]_0{}^a$ | |
buffer	pH	2	3
phosphate	6.0	$1.8^{b,d}$	
phosphate	8.0	$2.0^{b,d}$	$1.9^{b,d}$
borate	8.0	$1.3^{b,d}$	
borate	8.9	$1.3^{b,d}$	$2.0^{b,e}$

b. Thiacyclohexanes

| | | $-\Delta \log k_2/\Delta \log [I^-]_0{}^a$ | | |
buffer	pH	4	5	6
phosphate	7.0	$1.6^{c,e}$	$1.8^{c,d}$	
phosphate	8.0 $\{$	$1.5^{c,g}$	$1.7^{c,e}$	$1.9^{c,d}$
		$1.6^{b,f}$		
borate	8.0	$1.1^{c,d}$		$1.5^{c,d}$
borate	9.0	$1.0^{c,d,f}$	$1.1^{c,e}$	$1.9^{c,d}$

^{a} Second-order rate constants, k_2, calculated by dividing the pseudo-first-order rate constant, k_1, by [RSR']. Duplicate determinations in three to six different solutions $[I^-] = 0.01 - 0.06$ M. ^{b} 0.0250 M buffer. ^{c} 0.0125 M buffer. $^{d-g}$ Correlation coefficients: d, >0.999; e, 0.996; f, 0.997; g, 0.993.

cis isomer both the CH_3 and S–O groups are axial. The carbon atoms of *axial* methyl groups appear at higher field than their *equatorial* counterparts due to the syn-1,3-*diaxial* interactions between the *axial* methyl group and the *axial* protons of the ring. The methyl protons are also clearly distinguishable in the ^1H NMR, and their chemical shifts parallel the ^{13}C results.

Dependence of Rate on Buffer Concentration. In Figures 1 and 2 are plotted the values of rate constants k_2 (M^{-1} s^{-1}) vs. buffer concentrations. These plots allow an evaluation of the contribution of buffer mediation to the observed rates. At pH 8.0, the effect of borate buffer concentration on the rates of **2** (Figure 1a), **4** (Figure 2b), and **5** (Figure 2a) is very small. In contrast, an increase in phosphate buffer concentration causes a sizable increase in the rates of oxidation. For example, at 0.0125 M phosphate buffer, the ratio of the buffer catalyzed to the uncatalyzed rates are 3.5:1.0 for **5** and 1.0:1.0 for **4**, and for **2** in 0.0250 M phosphate buffer, the rate ratio is 9:1.

When **2**, **4**, or **5** is oxidized at pH 8.0, either borate or phosphate can be used as a buffer. The values of the rates can be extrapolated to zero molar buffer to give the buffer independent rate for each compound. The extrapolated rates were within experimental error.

The effect of pH and buffer species on the rate of oxidation of **2** at constant iodide and total buffer concentration is shown
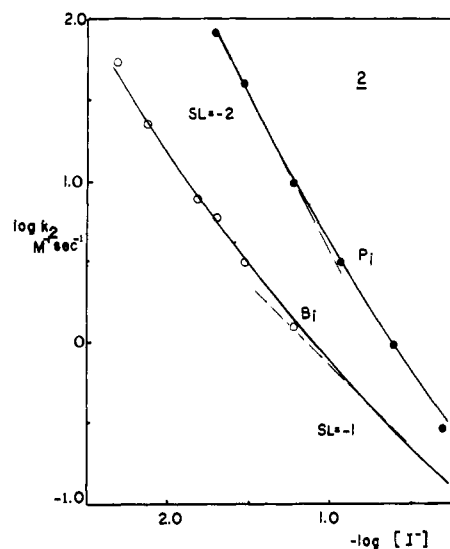
(13) Lambert, J. B.; Keske, R. G. *J. Org. Chem.* **1966**, *31*, 3429.

Figure 4. Log–log plots of the second-order rate constants of aqueous I_2 oxidation of **2** vs. $[I^-]$ (pH 8.0, 0.025 M buffer; $[R_2S] = 7.17 \times 10^{-4}$ M; $[I_3^-]_0 = (2-4) \times 10^{-5}$ M; 26.0 °C); ●, phosphate buffer, P_i; O, borate buffer, B_i. Solid lines are drawn through theoretical values (see Results and Discussion). Dashed lines indicate slopes of –1.0 and –2.0.
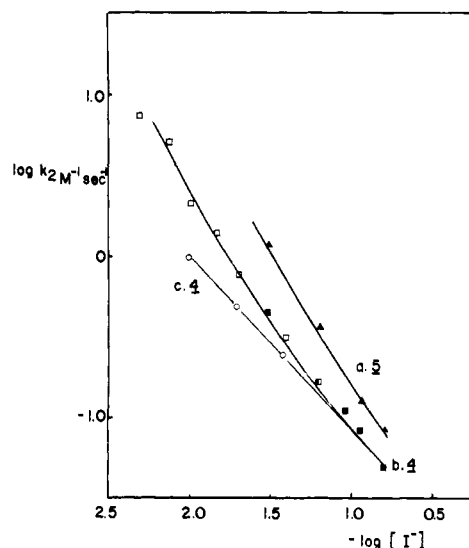

Figure 5. Plots used to determine the iodide dependence of the second-order rates of aqueous I_2 oxidation (pH 8.0, 0.0125 M buffer; $[R_2S] = (40-100) \times 10^{-5}$ M; [KI] + [KCl] = 0.060 M; $[I_3^-]_0 = (2-4) \times 10^{-5}$ M, 26.0 °C): △, 4-hydroxy-4-methylthiacyclohexane, **5**, phosphate, P_i; □, 4-hydroxythiacyclohexane, **4**, phosphate, P_i; O, 4, borate, B_i. The corresponding closed symbols are values in solutions where [KI] + [KCl] = 0.50 M. The equations for the curves are of the form $k_{obsd} = k_c[I^-]^{-2} + k_u[I^-]^{-1}$ (see Results): curve a, $k_c = 8.7 \times 10^{-4}$, $k_u = 6.3 \times 10^{-3}$; curve b, $k_c = 2.0 \times 10^{-4}$, $k_u = 6.5 \times 10^{-3}$; line c has a slope of –1.1.

in Figure 3. With increasing pH, the rate increases and then appears to level off. The theoretical curve was calculated from eq 1. The slope used in the equation was obtained from Figure

$$k_2 = k_2^0 + (\Delta k_2/\Delta[HPO_4^{2-}])[HPO_4^{2-}]$$
$$= 5.0 + 1740[HPO_4^{2-}] \; M^{-1} \; s^{-1} \quad (1)$$

1a where the value of $\Delta k_2/\Delta[buffer]_{total} = 1500$, but, since at pH 8.0, $[HPO_4^{2-}] = 0.86$ $[buffer]_{total}$, $\Delta k_2/\Delta[HPO_4^{2-}] = 1740$.

The effect of pH and buffer species on the rate of oxidation of **4** at constant iodide is more complex. Examination of Figure 2b indicates that the extrapolated value of k_2, k_{ext}, varies with pH and indicates specific hydroxide catalysis.

The Iodide Dependence of the Rate. The value of log k_2 vs. log $[I^-]_0$ are listed in Table I, along with their coefficients of correlation. For $[I^-]^n$ and $n = -1.0$ or -1.1, the data were plotted against
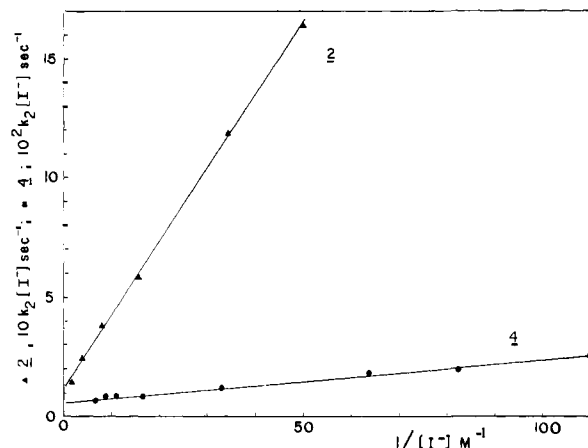
Figure 6. Plots of $k_2[I^-]$ vs. $[I^-]^{-1}$ (pH 8.0, phosphate buffer, 26.0 °C; $[I_3^-]_0 = (2-4) \times 10^{-5}$ M): a, $[2] = 7.17 \times 10^{-4}$ M, 0.025 M buffer; b, $[4] = (40-100) \times 10^{-5}$ M, 0.0125 M buffer.

the function $[I^-]^{-1}$, and when $n = -1.8$ to -2.0, the data were plotted against $[I^-]^{-2}$. These were linear plots which also passed through the origin. When $n = -1.3$ to -1.5, the plots of k_2 vs. the two functions were decidedly curved, as shown in Figures 4 and 5. The direction of the curvature suggests that the data be treated as a power series of the form

$$y = \sum_{n=0}^{i} a_n x^{-n}$$

The theoretical curves in Figures 4 and 5 were obtained by using a summation of the form $k'[I^-]^{-1} + k''[I^-]^{-2}$. Values of k' and k'' were determined by linear regression using the equation $k_2[I^-]$ $= k'$ and $k''[I^-]^{-1}$ as shown by the data replotted in Figure 6.

For the oxidation of **2** and **3** the rates exhibit iodide dependences of -2.0 and -1.9 in pH 8.0 phosphate. However, when **2** and **3** are oxidized in pH 9.0 borate, the iodide dependence of **3** is relatively unchanged, whereas the apparent dependence of the rate of **2** decreases to -1.3.

When the study of the I_2 oxidation of **2** was extended to higher concentrations of iodide, the apparent iodide dependence was decreased. The data, as shown in Figure 4, were correlated by eq 2 (in phosphate) and 3 (in borate). The parameters were

$$k_2 = 0.11[I^-]^{-1} + 0.031[I^-]^{-2} \tag{2}$$

$$k_2 = (6.3 \times 10^{-2})[I^-]^{-1} + (9.0 \times 10^{-4})[I^-]^{-2} \tag{3}$$

obtained from Figures 1a and 3 by assuming that the catalyzed rate was dependent on $[I^-]^{-2}$ and the uncatalyzed rate dependent on $[I^-]^{-1}$. The intercepts of the theoretical curves in eq 1–3 are 3.8 ± 0.9 M^{-1} s^{-1} as compared to the extrapolated value of 2.3 ± 0.6 M^{-1} s^{-1}.

Comparative Reactivity. Extrapolation of the borate data for the hydroxythiacycloalkanes **2, 4,** and **5** and of the phosphate data for the thiacycloalkanes **3** and **6** permits some comparison of relative rates in the absence of buffer. Relative overall rates in 0.03 M KI/0.03 M KCl at pH 8.0 are **2:5:4:3:6:** = 90:9:6:2:1. Because of the differences in the iodide dependences (Table I, Figures 4–7), the apparent rate enhancement of the hydroxy-thiacycloalkanes will increase at higher iodide concentrations.

From inspection of Figures 2, 5, and 7 it is observed that in phosphate buffer all three thiacyclohexane compounds **4, 5,** and **6** have similar absolute rates, e.g., differences of a factor of 2.5 at 0.0125 M phosphate. In contrast, the rate of **2** is always 40–100 times faster than the rate of **3** regardless of the presence or absence of phosphate (Figures 1 and 4).

Discussion

Effect of Phosphate Buffer. The simple thioethers **3** and **6** exhibit typical inverse second-order dependence in iodide ion in phosphate buffer. In contrast, the hydroxyl substituted thioethers **2, 4,** and **5** exhibit iodide dependences described by the two-term equation $k_2 = k_u[I^-]^{-1} + k_c[I^-]^{-2}$. The values of k_u and k_c are
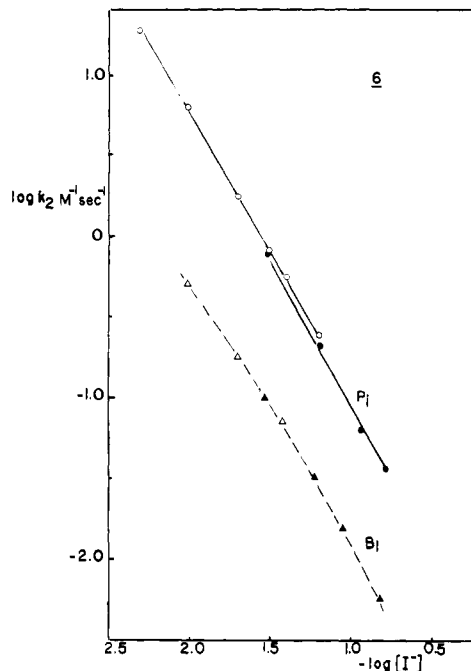

Figure 7. Plots used to determine the iodide dependence of the second-order rates of aqueous I_2 oxidation of **6** (pH 8.0, 0.0125 M buffer, 26.0 °C; $[R_2S] = (40-100) \times 10^{-5}$ M, $[I_3^-]_0 = (2-4) \times 10^{-5}$ M. The closed symbols are values in solution where $[KI] + [KCl] = 0.15$ M; the open symbols are values in solution where $[KI] + [KCl] = 0.06$ M: O, phosphate buffer, P_i; $\triangle$, borate buffer, B_i. The solid lines have slopes of -1.9.

obtained from the plots in Figures 1 and 2 and correspond to the buffer-independent rate and the buffer-catalyzed rate, respectively. The value of k_c is directly proportional to the buffer concentration and may include terms for all nucleophilic buffer species. Likewise, k_u may include terms for solvent-mediated, hydroxide, and intramolecular hydroxyl-catalyzed rates.

The change in the rate of oxidation of **2** in phosphate buffer over the pH range 6–9 is mainly due to the concentration of HPO_4^{2-} in solution at a given pH (Figure 3). Higuchi and Gensch[5] have previously shown that HPO_4^{2-} is the species responsible for the catalyzed oxidation of thiacyclopentane by I_2.

Effect of Borate Buffer. The rate of thioether oxidation in borate buffer normally represents the rate in the absence of buffer mediation.[2,4,5] For compounds **4** and **5** the absence of buffer mediation is manifest as an inverse first-order iodide dependence of the reaction rate (Table I). However, for compound **2** in borate, the rate has an apparent dependence of $[I^-]^{-1.3}$ as well as a very small dependence on the buffer concentration. This fractional iodide dependence suggests that the reaction follows two paths as indicated by $k_2 = k'[I^-]^{-1} + k''[I^-]^{-2}$. However, the ratio $k'_{:}k''$ = 70:1 is large which shows that the extent of the borate dependent path is small. Nevertheless, this behavior is unusual for borate and cannot be attributed to any specific effect. However, the aggregation of borate anions[14] as well as the known proclivity of borate to interact with alcohol groups may contribute to this anomaly.

(14) Ingri, N. *Acta Chem. Scand.* **1963**, *17*, 573, 581.

(15) (a) An alternate explanation for the intermolecular catalysis is that borate, acetate, and phosphate are acting as general base catalysts as in ref 15b and that proton transfer from the hydroxyl group occurs in the rate-determining step. It is difficult to explain how borate acting as a general base can change the observed order in iodide and why borate should have such low catalytic activity. (b) Swain, C. G.; Kuhn, D. A.; Schowen, R. L. *J. Am. Chem. Soc.* **1965**, *87*, 1553.

(16) Rosenfield, R. E., Jr.; Parthasarathy, R.; Dunitz, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 4860.

(17) The iodine complex is used in Scheme I because the complex $4 \cdot I_2$ has been isolated from aqueous solution and the preliminary X-ray analysis carried out. There is no evidence for I–I bond cleavage before the rate-determining step in path A. Olmstead, M. M., private communication.

In pH 9 borate buffer it appears that the simple thioethers **3** and **6** continue to react via a path which is inverse second order in iodide. This observation is consistent with the established mechanism for the iodine oxidation of simple thioethers in basic solutions. At pH 8.0 in borate buffer, however, the inverse second-order dependence for **6** occurs only at higher iodide concentrations (Figure 7). This trend has also been observed for the I_2 oxidation of thiacyclopentane[5a] at pH 8 in the absence of buffer and is in the direction opposite to that predicted by a simple two-path mechanism.

From all the evidence available it appears that at higher iodide concentrations, the iodide dependence n equals -1 for hydroxy-thiacycloalkanes **2**, **4**, and **5**, and equals -2 for thiacycloalkanes.

Kinetics and Mechanism of Hydroxyl Participation. For clarity an abbreviated kinetic scheme which is consistent with the data is presented below. A more detailed mechanism which also accounts for the stereoselectivity of the products and the observed intermediate, **1**, will be discussed later. The simplest explanation of the changes in iodide dependence of the rate laws observed for the hydroxycycloalkanes **2**, **4**, and **5** involves reaction by two parallel paths, A and B, which proceed to give oxidation products in which the hydroxyl and sulfoxide groups are trans. Since the kinetics are monitored by triiodide absorbance, the first step is always the triiodide equilibrium K_1. A simple inverse first-order dependence on iodide is due to this equilibrium.

$$I_3^- \rightleftharpoons I_2 + I^- \qquad (K_1)$$
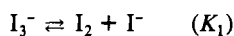
An iodine–thioether complex[17] is formed in equilibrium.

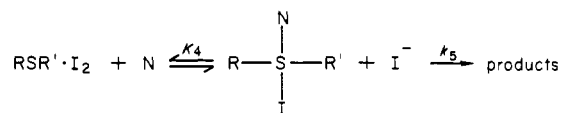$$I_2 + RSR' \rightleftharpoons RSR' \cdot I_2 \qquad (K_2)$$

It is this complex which decomposes via two major paths. In path A there are no further equilibria involving iodide loss before the rate-determining step

$$\text{path A:} \quad RSR' \cdot I_2 \xrightarrow{k_3} \text{products}$$
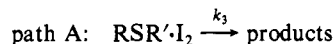
and the kinetic expression is

$$d[RSR']/dt = -[RSR'][I_2]K_2k_3 =$$
$$-[RSR'][I_3^-]K_1^{-1}K_2k_3[I^-]^{-1}$$
$$= d[I_3^-]/dt$$

Path **B** is first order in buffer (N) and includes an equilibrium involving the loss of one iodide ion before the rate-determining step.

$$RSR' \cdot I_2 + N \xrightarrow{k_4} R\text{—}\overset{\overset{\displaystyle N}{|}}{\underset{\underset{\displaystyle I}{|}}{S}}\text{—}R' + I^- \xrightarrow{k_5} \text{products}$$

The kinetic expression for path B is

$$d[RSR']/dt = -[RSR'][I_2][N]K_2K_4[I^-]^{-1}k_5$$
$$= -[RSR'][I_3^-][N]K_1^{-1}K_2K_4[I^-]^{-2}k_5$$
$$= d[I_3^-]/dt$$

The total observed rate is

$$d[I_3^-]/dt = -[RSR'][I_3^-]K_1^{-1}K_2(k_3[I^-]^{-1} + K_4k_6[N][I^-]^{-2})$$

which is of the form demonstrated by the plots in Figure 6 and is used to generate the theoretical curves in Figures 4 and 5.

A detailed mechanism for the thioether oxidation of **2**, **4**, and **5** is given in Scheme I. The two paths disjoin after the formation of the iodine–thioether complex. This complex rather than an iodosulfonium salt is suggested to minimize solvent and buffer interaction at this step which, in turn, could lead to the cis product. In path A the transannular hydroxyl group attacks the sulfur atom in the rate-determining step. In a sequence of steps, the intermediate may undergo deprotonation, alkoxysulfonium ion formation, and, finally, hydrolysis to the trans product. In the reaction of **2**, the intermediate alkoxysulfonium ion, **1**, has been isolated and characterized.[3] Path B occurs in proportion to the

Scheme I. Proposed Mechanism for the Aqueous I_2 Oxidation of Hydroxythiacycloalkanes 2, 4, and 5
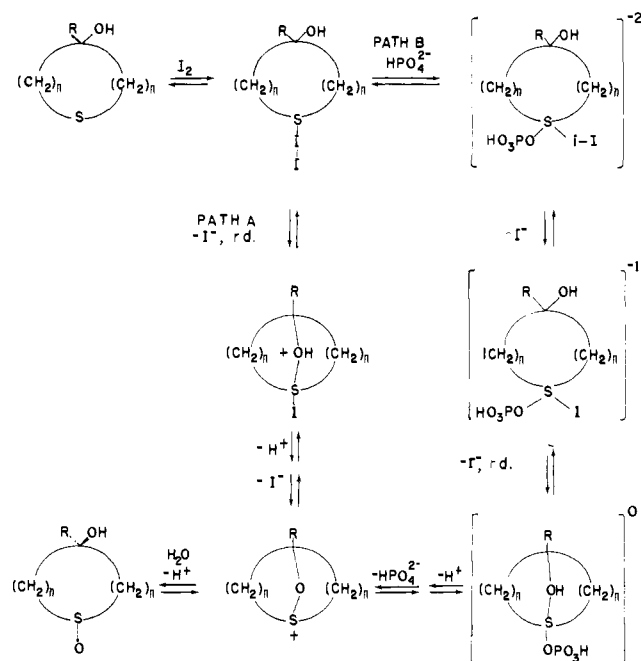
observed catalysis by buffer (Figure 1 and 2) and is inverse second order in iodide. In the scheme HPO_4^{2-} is shown as the nucleophile since in the reaction of **2**, catalysis is mainly due to HPO_4^{2-}. The iodine complex reacts with buffer and one iodide ion dissociates from this sulfurane. In the rate-determining step, the transannular hydroxyl group displaces the remaining iodide ion, and subsequent intermediates are formed which lead to the trans product. Thus, only *trans*-5-hydroxythiacyclooctane 1-oxide is the product from **2** and >92% of the sulfoxide with the trans arrangement of the OH and S–O groups is isolated from both **4** and **5**. For **2** any path which involves reaction with water and/or buffer in a trans-diaxial relationship to the departing iodide may be discarded since the sulfoxide resulting from this interaction would be the diastereomer. Additionally, this mode of reaction in **4** (OH equatorial) would give the trans isomer, but in **5** (CH₃ equatorial, OH axial[18]) would give the isomer with the cis arrangement of the OH and S–O substituents.

The structural features of the intermediates must also be consistent with the principles of microscopic reversibility and the preferred geometry of hypervalent sulfur. We suggest the following pattern. (a) Electrophilic attack by iodine on the thioether groups occurs perpendicular to the C_α–S–C_α plane. This geometry is consistent with the results of Rosenfeld et al.[16] and was confirmed by a crystal structure of $4 \cdot I_2$.[17] (b) In path B nucleophilic attack on the iodine complex by buffer occurs coaxial with a C–S bond due to steric hindrance to axial approach. (c) Bonding occurs between the σ^* orbital of the C–S bond and an oxygen atom of the buffer. (d) The negative charge which builds up on the complex because of buffer coordination promotes the loss of an iodide ion. Iodide loss does not occur at this stage in the absence of specific buffer coordination. (e) The rate-determining step in both paths involves attack by the hydroxyl group and elimination of iodide in a trans-diaxial displacement. Some specific hydroxide catalysis may assist hydroxyl participation and complete deprotonation leads to the alkoxysulfonium salt. (f) The step leading to product involves a trans-diaxial displacement of the alkoxy group by solvent to give the trans alcohol–sulfoxide exclusively.

Path A resembles the mechanism proposed for the aqueous I_2 oxidation of 5-methyl-1-thia-5-azacyclooctane.[1] Although the rate law for path B is similar to that of simple thioethers, including **3** and **6** in the present study, this is the first time that a direct

---

(18) Hirsch, J. A.; Allinger, N. L.; Eliel, E. L. "Topics in Stereochemistry"; Interscience: New York, 1967; Vol. 1.

displacement of iodide could *not* be invoked to account for the intermediate and products obtained.

Regarding the modest rate accelerations of ca. 45 for **2** and ca. 6–9 for **4** and **5**, it should be recalled that in an analogous carbocyclic system,[19] *cis*-and *trans*-4-hydroxycyclohexyl chloride react at the same rate in aqueous base, although 7-oxobicyclo-[2.2.1] cycloheptane is the major product only from the trans isomer. In this 6-membered ring, the transannular 4-hydroxy group participates after the rate-determining step. Formation of the bridged alkoxysulfonium intermediate was proposed to account for the acceleration of 150 in the solvolysis rates of the *trans*- vs. the *cis-p*-toluenesulfonates of 4-hydroxythiacyclohexane 1-oxide.[20] Considering that an axial OTs group undergoes solvolysis four times faster than an equatorial OTs group, the additional rate enhancement is ca. 40 due to the formation of the bridged intermediate formed by sulfoxide participation. In general only a moderate anchimeric assistance would be expected in path A (Scheme I).

Evidence for intramolecular catalysis in thioether oxidation has now been presented when SR, NR_2, OH, and CO_2H[21] are neighboring groups. Quantitative determinations of the influence

of other neighboring groups on oxidation at divalent sulfur atoms are in progress.

Conclusion

The kinetics of the hydroxythiacycloalkane compounds **2**, **4**, and **5** suggest that oxidation occurs via two pathways. Both paths involve sulfurane formation and rate-determining hydroxyl participation followed by rapid decomposition of the bridged intermediate. Under ideal circumstances the bridged alkoxysulfonium salt can be precipitated from solution. This work confirms the hydroxyl group participation which was postulated to explain the lowering of the oxidation potential of **2** by 0.6 V relative to simple thioethers.[22] The stereochemistry of the products are also consistent with the formation of *trans*-4-hydroxythiacyclohexane 1-oxide from the reaction of **4** with *tert*-butyl hypochlorite in the nonpolar solvent CH_2Cl_2.[8]

(19) Heine, H. W. *J. Am. Chem. Soc.* **1957**, *79*, 6268.
(20) Martin, J. D.; Uebel, J. J. *J. Am. Chem. Soc.* **1964**, *86*, 2936.
(21) Tagaki, W.; Ochiai, M.; Oae, S. *Tetrahedron* **1968**, *58*, 6131.

(22) Glass, R.; Duchek, J.; Klug, J.; Wilson, G. *J. Am. Chem. Soc.* **1977**, *99*, 7349.

Intramolecular General-Base Catalysis of Schiff-Base Hydrolysis by Tertiary Amino Groups

Tadashi Okuyama,* Hiroshi Shibuya, and Takayuki Fueno

Contribution from the Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan. Received June 22, 1981

Abstract: Hydrolysis of a series of Schiff bases (**1**) derived from benzophenone and various amines has been studied kinetically in aqueous solution. A linear correlation of the log of the rate constants for the water reaction with the Schiff base pK_a (slope −0.70) shows large positive deviations for Schiff bases derived from (2-aminoethyl)diethylamine (**1e**), *N*-(2-aminoethyl)morpholine (**1f**), *N*-(2-aminoethyl)piperazine (**1h**), and 2-(aminomethyl)pyridine (**1i**) but small deviations for Schiff bases from *N*-(3-aminopropyl)morpholine (**1g**) and 2-(2-aminoethyl)pyridine (**1j**). The deviations found are attributed to intramolecular general-base catalysis of the water reaction by the internal tertiary amino groups. Magnitudes of the rate enhancement are correlated well with pK_{a1} of the internal catalyst ($\beta = 0.49$). Effective concentrations of the internal bases are estimated to range from 340 (**1e**) to 40 M (**1i**).

The importance of Schiff bases as intermediates in many of the enzymatic transformations of both carbonyl compounds and amines[1] has generated a great deal of interest in the mechanism of formation and hydrolysis of these compounds. General features of the mechanism of Schiff-base hydrolysis are now well understood.[2] Although intramolecular catalysis has been extensively studied on a variety of reactions as a relevant model for the catalytic action of various enzymes,[3] examples of intramolecular catalysis in the Schiff base hydrolysis are limited. Intramolecular general-base catalysis by an ionized *o*-hydroxy group was once suggested for the hydrolysis of Schiff bases derived from salicylaldehyde[4] and 3-hydroxypyridine-4-carboxaldehyde[5] but subse-

quently demonstrated to be improbable.[6] Pollack et al.[7,8] have recently presented evidence that the hydrolysis of Schiff bases derived from cyclohexene-1-carboxaldehyde is catalyzed by an internal carboxylate ion.

Since we have found indications that some internal amino groups catalyze the Schiff-base hydrolysis during our investigations of the amine catalysis of isomerization of a β,γ-unsaturated ketone,[9] systematic studies of catalysis by internal amino groups have been conducted for the hydrolysis of Schiff bases (**1a–j**) derived from benzophenone. Tertiary amino groups attached at the β-position from the imino nitrogen atom showed marked intramolecular general-base catalysis of water attack on the protonated Schiff bases $1H^+$, and the results of our studies are described herein.

(1) Snell, E. E.; di Mari, S. J. In "The Enzymes", 3rd ed.; Boyer, P. D., Ed.; Academic Press: New York, 1970; Vol. 2, pp 335–370.
(2) (a) Jencks, W. P. *Prog. Phys. Org. Chem.* **1964**, *2*, 63–128. (b) Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969; pp 490–496.
(3) (a) Bruice, T. C. In "The Enzymes", 3rd ed.; Boyer, P. D., Ed.; Academic Press: New York, 1970; Vol. 2, pp 217–279. (b) Kirby, A. J.; Fersht, A. R. *Prog. Bioorg. Chem.* **1971**, *1*, 1–82.
(4) Reeves, R. L. *J. Org. Chem.* **1965**, *30*, 3129–3135.
(5) French, T. C.; Auld, D. S.; Bruice, T. C. *Biochemistry* **1965**, *4*, 77–84.

(6) Bruyneel, W.; Charette, J. J.; DeHoffmann, E. *J. Am. Chem. Soc.* **1966**, *88*, 3808–3813.
(7) Kayser, R. H.; Pollack, R. M. *J. Am. Chem. Soc.* **1977**, *99*, 3379–3387.
(8) Pollack, R. M.; Kayser, R. H.; Damewood, J. R., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 8232–8237.
(9) Okuyama, T.; Kitada, A.; Fueno, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2358–2361.