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Chemical Reactions Mediated by Heavy Metal Ions. 1. The Mercury(II)-Promoted Hydrolysis of Benzaldehyde *O*-Ethyl *S*-Ethyl Acetal

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This is a kinetic study of the hydrolysis of an acyclic *O,S*-acetal promoted by heavy metal ions. The acyclic structural feature is important because it precludes the potential return of the sulfur moiety at the spectral concentrations at which experiments are conducted, a possibility which clouds some of the interpretations of earlier work. Results of this study of the hydrolysis of benzaldehyde *O*-ethyl *S*-ethyl acetal establish that (1) mercury(II) acts as a reagent, not a catalyst in the hydrolysis reaction, (2) the rate-limiting step can be either of the two steps shown in Scheme I, depending on the concentration of mercury(II) relative to the acid, and (3) the state of complexation of mercury(II) is critical to its reactivity. Experiments are reported defining the rate-limiting step under a wide variety of reaction conditions. The second-order rate constants measured for promotion of the hydrolysis by $HgCl^+$, $HgCl_2$, and $HgCl_3^{-1}$ are 10^9, 10^6, and 10^4 M^{-1} s^{-1}, respectively. The second-order rate constant for the acid-catalyzed breakdown of benzaldehyde ethyl hemiacetal is 660 M^{-1} s^{-1}.

Introduction

Hydrolyses of *O,S*-acetals have received considerable attention for a variety of reasons.[1a] This functionality is used by synthetic organic chemists as a protecting or blocking group, and its convenient removal is vital to its successful use. In addition, the mixed acetal functionality exists in a variety of biologically important molecules, and reactions targeting sulfur are of important consequence in such systems.[2,3] Finally, the reactions of heavy metals acting as Lewis acid reagents or catalysts are of fundamental importance if the knowledge acquired from the extensive studies of Brønsted acids is to be extended.

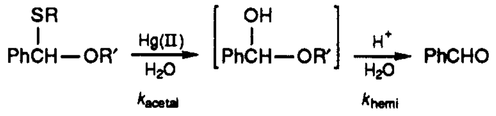
The present study reports acyclic *O,S*-acetal hydrolysis promoted by heavy metal ions. The acyclic structural feature is important because it precludes the potential return of the sulfur moiety at the spectral concentrations at which experiments are conducted, a possibility which clouds some of the interpretations of earlier work. Previous studies of *O,S*-acetal hydrolyses promoted by heavy metal ions utilized cyclic organic substrates[1,4] and did not clearly delineate rate-determining hemiacetal breakdown from rate-determining *O,S*-acetal carbon–sulfur bond breaking (k_{hemi} and k_{acetal} in Scheme I).

Our results establish that (1) mercury(II) is a reagent, not a catalyst in the hydrolysis reaction, (2) the rate-limiting step can be either of the two steps shown in Scheme I, depending on the concentration of mercury(II) relative to the acid, and (3) the state of complexation of mercury(II) is critical to its reactivity.

Experimental Section

Materials. The *O,S*-acetal was synthesized by procedures reported earlier.[5] Benzaldehyde diethyl acetal was prepared from benzaldehyde and triethylorthoformate.[6a] Treatment of the diethyl acetal with thionyl chloride made the α-chloro ether, which, after removal of volatiles, was vacuum-distilled into a cold solution of ethyl thiolate in DMF (prepared just prior to use by slow addition of ethane thiol to a slight stoichiometric excess [10%] of NaH in DMF). The vacuum-distilled final product was characterized by proton magnetic resonance and UV spectroscopy.

Scheme I



All reagents were reagent grade and used as supplied, except that the perchloric acid used for conditions generating $<10^{-3}$ M chloride ion concentration was supplied by GFS Chemicals: this 70% perchloric acid had been double-distilled from Vycor and assayed as containing <0.000 01% halide (as chloride) and <0.000 001% heavy metals (as lead).

Distilled water was further purified for these experiments using a Milli-Pore Milli-Q water purification system, complete with charcoal and ion-exchange cartridges; typical resistance of the water so purified was >10 MΩ Cm.

Kinetic Methods. The standard, general computational procedures used have been described previously.[6] All rate constants were obtained using a Dionex triple-mixer stopped-flow spectrophotometer, using a Nicolet Explorer IIIA oscilloscope to acquire time-absorbance data at λ_{max} for the major chromophore in the product (benzaldehyde, λ_{max} = 249 nm). Repetitive overlay UV scans during the course of the hydrolysis (obtained using a HP 8451A diode array spectrometer) showed the smooth increase in absorbance expected for the formation of benzaldehyde from the weak chromophore of the *O,S*-acetal. The Nicolet Explorer IIIA oscilloscope was interfaced to a HP 9825T desktop microcomputer equipped with a HP 7470A printer-plotter.[7]

Rate constants reported are means of four kinetic runs, each consisting of a calculation based on 50–100 points covering 3 half-lives of reaction time. The software contains an adaptation of a classic[11] "optimization" subroutine, which treats the "infinity" absorbance as a variable in order to maximize the linear fit of the other data points to the first-order kinetic equation. It has

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Scheme II

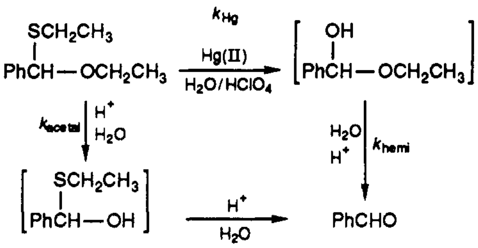

Table I. Observed Rate Constants in the Presence and Absence of Hg(II)[a]

$[HClO_4]$	$[Hg(II)] = 0$ k_{obs}[b]	$[Hg(II)] = 1.0 \times 10^{-4}$ k_{obs}[c]	$[Hg(II)] = 1.0 \times 10^{-5}$ k_{obs}[d]	$[Hg(II)] = 5.0 \times 10^{-6}$ k_{obs}[e]
0.0010		0.621		
0.0020		1.39		1.36
0.0030		1.98		
0.0040		2.59		
0.0050		3.23		
0.0100		6.45	5.04	4.85
0.0200			8.01	7.69
0.0500	0.0411	32.9	17.6	16.5
0.100	0.0755	57.7	28.6	26.7
0.200			46.4	29.5
0.250	0.256			
0.500	0.604		57.4	28.8
1.00	1.78		59.4	29.8
1.50	3.61			
2.00	7.43			

[a] k_{obs}, units s^{-1}, 25 °C; 249 nm; [*O*,*S*-acetal] = 5.0×10^{-6}; average of >3 kinetic runs. [b] $k_{H^+} = 1.1\ M^{-1}\ s^{-1}$ (lit.[5] $1.3\ M^{-1}\ s^{-1}$ at $\mu = 1.0$ (KCl)). [c] $[HgCl_2] = 1.0 \times 10^{-4}$ M, $[NaCl] = 1.0 \times 10^{-4}$ M. [d] $[HgCl_2] = 1.0 \times 10^{-5}$ M, $[NaCl] = 1.0 \times 10^{-4}$ M. [e] $[HgCl_2] = 5.0 \times 10^{-6}$ M, $[NaCl] = 1.0 \times 10^{-4}$ M, [*O*,*S*-acetal] = 2.5×10^{-6} M.

been shown[12] that this optimization process does a good job of calculating the pseudo-first-order rate constant at the initial concentration condition in cases where ideal pseudo-first-order concentration conditions are not employed (e.g., where reactant ratios are 2:1, rather that the ideal 10:1). Of course, when the optimization calculations are employed under ideal conditions, the changes in "fit" are within experimental error. We have used this same sort of calculation previously,[13] in cases where the "infinity" value was not experimentally accessible.

Results

Rate-Limiting Step Criteria. Experiments were conducted in the presence and absence of Hg(II) so as to assure that the expected kinetic orders could be experimentally observed. The reaction to be studied is the mercury-promoted hydrolysis of the *O*,*S*-acetal; production of product requires acid for the breakdown of the hemiacetal intermediate to be fast relative to the mercury reaction. However, the *O*,*S*-acetal hydrolyzes slowly by an acid-catalyzed pathway. These competing processes are diagrammed in Scheme II.

The rate constants are designated as k_{acetal} for the acid-catalyzed hydrolysis of the *O*,*S*-acetal, k_{hemi} for the acid-catalyzed breakdown of the hemiacetal, and k_{Hg} for the mercury-promoted step. The k_{acetal} process has been shown to proceed as Scheme II indicates (via the hemithioacetal), with the rate-limiting step being the formation of the hemithioacetal.[5]

The data in Table I show that in the absence of mercury, k_{acetal} exhibits a first-order dependence on acid; a plot of k_{acetal} vs the Hammett acidity function[8] produces a second-order rate constant, $k_{H^+}(\text{acetal}) = 1.1\ M^{-1}\ s^{-1}$, in excellent agreement with the reported value[5] of $1.3\ M^{-1}\ s^{-1}$.

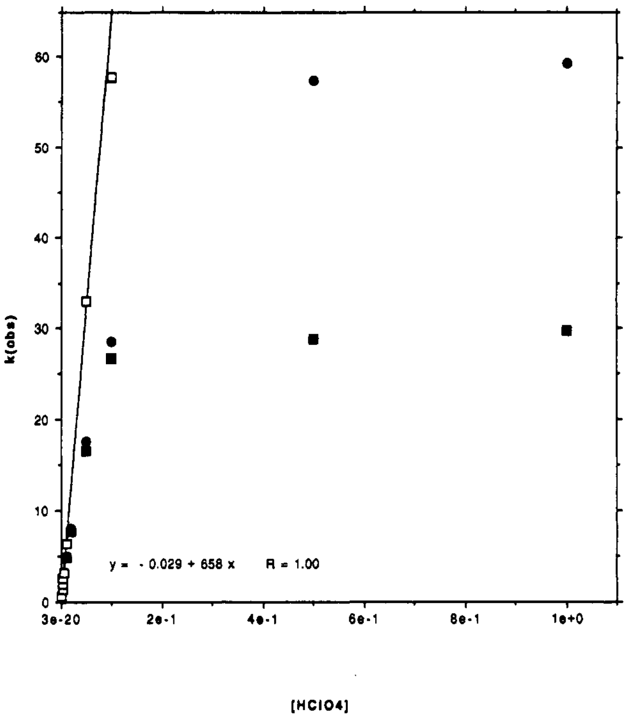

Figure 1. Mercury(II) and acid dependence of the hydrolysis of benzaldehyde *O*-ethyl *S*-ethyl acetal. (□) k_{obs} at $[HgCl_2] = 1.0 \times 10^{-4}$ M; (●) k_{obs} at $[HgCl_2] = 1.0 \times 10^{-5}$ M; (■) k_{obs} at $[HgCl_2] = 5.0 \times 10^{-6}$ M. Slope of the line generated by rate-limiting hemiacetal breakdown is 660 $M^{-1}\ s^{-1}$.

Similarly, at higher [Hg(II)] the observed rate constant exhibits a first-order dependence on acid (at lower $[H^+]$), indicating that the rate-limiting step under these conditions is hemiacetal breakdown. In order to study the k_{Hg} process, the mercury concentration must be sufficiently low and the acid concentration sufficiently high to assure that $k_{hemi} \gg k_{Hg}$. The expected changeover in rate-limiting step can be seen in the data reported at $[HgCl_2] = 1 \times 10^{-5}$ and 5×10^{-6} M. The kinetic equations, based on Scheme II and Table I, are:

$$k_{acetal} = k_{H^+}(\text{acetal})[H^+] \qquad (1)$$

$$k_{hemi} = k_{H^+}(\text{hemi})[H^+] \qquad (2)$$

$$k_{Hg} = k_{Hg(II)}[Hg(II)] \qquad (3)$$

The values of the second-order rate constants defined by eqs 2 and 3 can be calculated from a plot of Table I data, as shown in Figure 1. These values are:

$$k_{H^+}(\text{hemi}) = 660\ M^{-1}\ s^{-1}$$

$$k_{Hg(II)} = 6 \times 10^{6}\ M^{-1}\ s^{-1}$$

The value of $k_{H^+}(\text{hemi})$ calculated from data in Table I (25 °C and essentially zero ionic strength) is in excellent agreement with the value of 940 $M^{-1}\ s^{-1}$ reported at 30 °C at $\mu = 0.1$.[9] The acid concentration can now be adjusted so as to assure that k_{Hg} is the process being measured; an experimental check of the reaction conditions is that the observed rate exhibits first-order dependence on [Hg(II)] and zero-order dependence on $[H^+]$. These criteria assure that the data reported in Table III are for rate-limiting k_{Hg}.

Stoichiometric Requirement of Mercury. The kinetic solutions do not change appearance during the course

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Table II. Required Stoichiometry of Hg(II)-Promoted Hydrolysis of Benzaldehyde *O*-Ethyl *S*-Ethyl Acetal[a]

$10^5[HgCl_2]$	$[HgCl_2]/[O,S\text{-acetal}]$	final absorbance[b]
0.00	0.00	0.000
0.25	0.25	0.056
0.50	0.50	0.109
0.75	0.75	0.158
1.00	1.00	0.199
2.00	2.00	0.224
3.00	3.00	0.225

[a] 25 °C; 249 nm; [*O*,*S*-acetal] = 1.0×10^{-5} M; [NaCl] = 1.0×10^{-3} M; [$HClO_4$] = 0.10 M. [b] Average of the final absorbances of two kinetic runs.

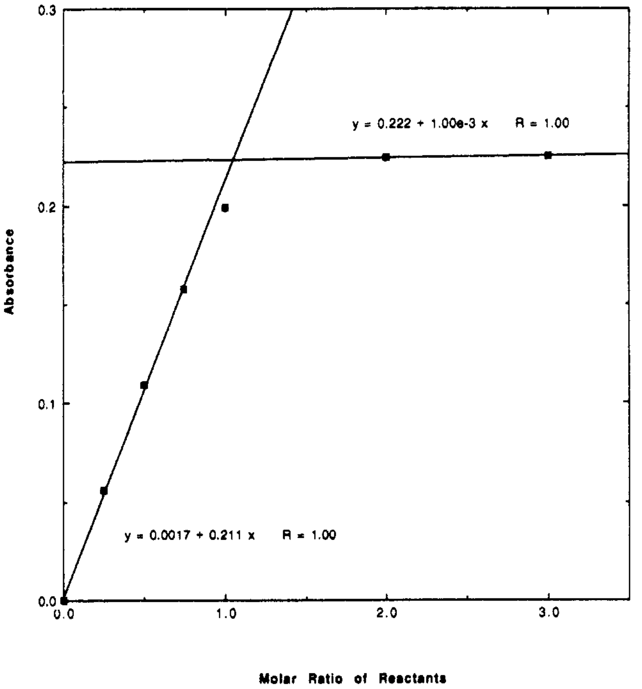


Figure 2. Spectrometric titration of benzaldehyde *O*-ethyl *S*-ethyl acetal with $HgCl_2$ (data from Table II). Line of zero slope intersects line defined by Beer's law at $[HgCl_2]/[O,S\text{-acetal}] = 1.05$.

of hydrolysis, raising the question as to whether the mercury is behaving as a reagent (i.e., inactivated during the hydrolytic reaction) or as a catalyst (i.e., active form is regenerated in the acidic solvent). To address this question, a spectrometric titration was performed, with the results summarized in Table II. When mercury is the limiting reagent, the quantity of product produced is dependent upon the mercury concentration in accord with Beer's law; however, when mercury is in excess the quantity of product produced is limited by the quantity of *O*,*S*-acetal. As Figure 2 clearly shows, the change from limiting to excess occurs at a $[HgCl_2]/[O,S\text{-acetal}]$ ratio of 1.05 (i.e., unity). Thus the mercury is effectively removed from the reaction scenario upon reaction with the *O*,*S*-acetal and the stoichiometry required is *O*,*S*-acetal: mercury = 1:1. This is consistent with formation of a mercury monothiolate complex, which remains in solution at these spectral concentrations.

Discussion

This study of the mercury-promoted hydrolysis of benzaldehyde *O*-ethyl *S*-ethyl acetal is important because the acyclic structure of the *O*,*S*-acetal precludes any sort of return or interaction between substrate and leaving group at the spectral concentrations employed—once the leaving group has indeed left the reaction center it is effectively removed from the reaction scene. As shown in the results, the thiol group and the mercury are removed together as the monothiolate complex.

Table III. Dependence of Hg(II)-Promoted Hydrolysis of *O*,*S*-Acetal on [Cl^-][a]

[NaCl]	$10^5[HgCl_2]$	[$HClO_4$][b]	k_{obs}[c]
0.0001	1.00	0.500	59.7
0.0010	1.00	0.250	29.3
0.0100	1.00	0.250	22.2
0.0200	1.00	0.250	16.5
0.050	1.00	0.250	8.25
0.100	1.00	0.250	4.24
0.250	5.00	0.100	1.43
0.500	5.00	0.100	0.749
1.00	5.00	0.010	0.374
1.50	5.00	0.010	0.218
2.00	5.00	0.010	0.124
2.50	25.0[d]	0.010	0.466[d]

[a] 25 °C; 249 nm; [*O*,*S*-acetal] = 5.0×10^{-6} M. [b] [$HClO_4$] selected to assure Hg(II)-promoted reaction is rate-determining. [c] s^{-1}, average of >3 kinetic runs. [d] [$HgCl_2$] increased 5-fold to generate convenient k_{obs}; plotted k_{obs} value is 0.093.

Discussion of the reaction mechanism requires knowledge of the reactive forms of the reagents involved in the reaction. In the case of mercury(II), the presence of chloride ion complicates the reaction scenario because of the equilibria shown in Scheme III. While the equilibrium constants are known,[10] the reported error limits require that our data lose more than one significant digit in the calculations to follow. The k_{Hg} defined by eq 3 is actually a composite rate constant; it is the sum of terms comprised of each of the rate constants for each of the five states of mercury defined in Scheme III, multiplied by the respective concentrations. This situation is diagrammed in Scheme IV.

Scheme III

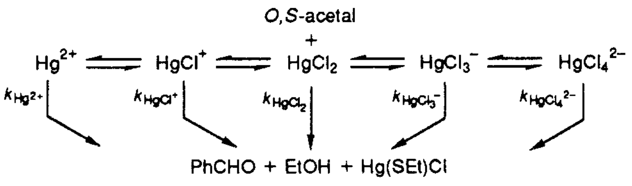
$$\begin{aligned} Hg^{2+} + Cl^- &= HgCl^+ & \log K_1 &= 6.74 \\ HgCl^+ + Cl^- &= HgCl_2 & \log K_2 &= 6.48 \\ HgCl_2 + Cl^- &= HgCl_3^- & \log K_3 &= 0.85 \\ HgCl_3^- + Cl^- &= HgCl_4^{2-} & \log K_4 &= 1.00 \end{aligned}$$

Inspection of Schemes III and IV and eq 4 leads to the

$$k_{Hg} = k_{Hg^{2+}}[Hg^{2+}] + k_{HgCl^+}[HgCl^+] + k_{HgCl_2}[HgCl_2] + k_{HgCl_3^-}[HgCl_3^-] + k_{HgCl_4^{2-}}[HgCl_4^{2-}] \quad (4)$$

obvious conclusion that the pseudo-first-order rate constant measured for the mercury-promoted hydrolysis, k_{Hg}, will be a function of the chloride concentration provided the five mercuric species exhibit different reactivities. The change in k_{Hg} with changing [Cl^-] is recorded in Table III. (k_{obs} is used in the table to emphasize that these are experimental numbers: k_{Hg} is the k_{obs} for rate-limiting mercury-promoted hydrolysis, which is true for all Table III data.) Data could be collected at [Cl^-] < 10^{-4} M because of the mixing limitations of the stopped-flow instrument. The value of k_{Hg} varies 600-fold and is most usefully displayed in Figure 3 as a plot of log k_{obs} vs log [Cl^-]. Using the literature values for the complexation constants

Scheme IV



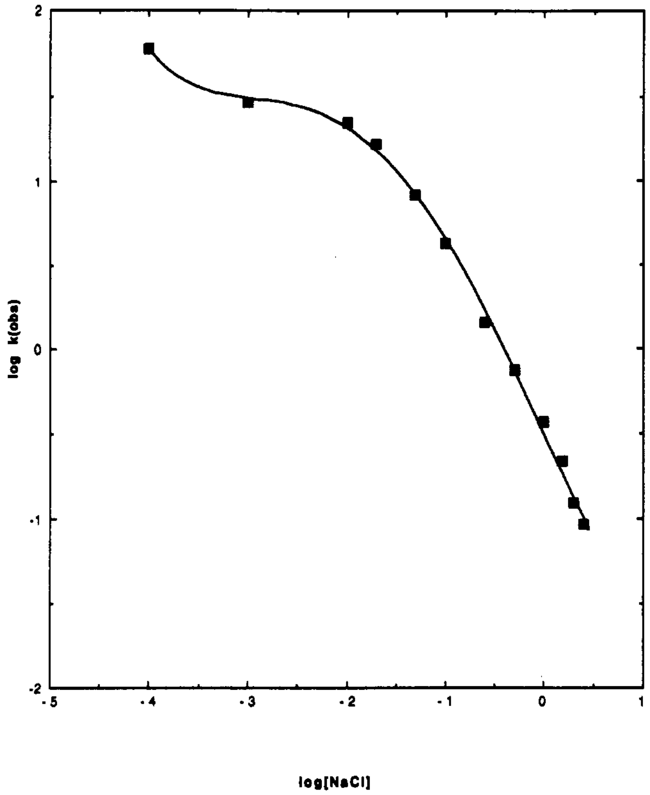


Figure 3. Dependence of k_{obs} on [Cl$^-$] for mercury(II)-promoted hydrolysis. The second-order rate constants listed in Table IV generate the line drawn through the experimental points plotted from Table III.

Table IV. Second-Order Rate Constants for the Mercury-Promoted Hydrolyses of Benzaldehyde *O*-Ethyl *S*-Ethyl Acetal[a]

$k_{Hg^{2+}} = 10^9$ M^{-1} s^{-1} [b]
$k_{HgCl^+} = 1 \times 10^9$ M^{-1} s^{-1}
$k_{HgCl_2} = 1 \times 10^6$ M^{-1} s^{-1}
$k_{HgCl_3^-} = 2 \times 10^4$ M^{-1} s^{-1}
$k_{HgCl_4^{2-}}$ cannot be distinguished from zero[c]

[a] Calculated from data in Table III, based on eq 4 and Scheme III. [b] Not calculable from Table IV data, but represents the diffusion limit.[14] [c] The value is not zero; it is not calculable from the range of data, which is limited by solubility, salt effects, etc.

(Scheme III), a best fit of our data to eq 4 was constructed. Because of (1) the substantial differences in the complexation constants and (2) the "plateau" region arising from the dominance of $HgCl_2$ as both a reactive reagent and major species, the fit is easily done using SuperCalc 3 on an IBM PC. The second-order rate constants defined by eq 4 are listed in Table IV; their certainty is less than one significant digit because of the complexation constants on which their calculation is based.

Eigen and Eyring[14] measured the rate of reaction of $HgCl^+$ with Cl$^-$ in water, recommending a value of 7×10^9 M^{-1} s^{-1} as the diffusion limit. Thus the rate of 1×10^9 M^{-1} s^{-1} calculated for reaction of $HgCl^+$ with the *O,S*-acetal in water seems to be at the diffusion limit, considering the uncertainties in complexation constants, the uncertainties in Eigen's value, and the difference in size between chloride and *O,S*-acetal. Hence the value of $k_{Hg^{2+}}$ is listed as 10^9 M^{-1} s^{-1}, indicating that it is at the diffusion limit as well. Our data does not afford a calculated value, since at 10^{-4} M chloride the concentration of Hg^{2+} is much less than the concentration of $HgCl^+$, which also reacts at the diffusion limit; however, the presumption that it reacts at the diffusion limit is safe.

Scheme V

The range in reactivity of 4 orders of magnitude shown in Table IV is striking; certainly reactions in which mercury is a reagent require careful control of ligand concentrations. It seems clear that application of simple Lewis acid/base concepts qualitatively explains the reactivities observed: As the Lewis acid center (mercury(II)) is progressively neutralized by a basic ligand (chloride), the metallocomplex becomes progressively less reactive. In this model, sulfur is simply a much more effective Lewis base toward mercury(II), presumably because it is a "softer" base than chloride and thus is a better "match" for the soft mercury(II) center. We are currently pursuing experiments directed at quantifying these concepts, which will require a considerable data set.

The large reactivity differences of Table IV, coupled with the huge deactivating effect of the thiolate ligand, explains why the alkylmercury halide substrates must be incubated in a buffer containing thiol prior to being a suitable substrate for bacterial organomercurial lyase:[15a] unless the mercury(II) is inactivated by forming a thiolate complex, it does inactivate the enzyme rather than serving as substrate. Indeed, the substrate for the enzyme is actually the alkylmercury thiolate species; in the absence of the thiolate ligand, the mercury(II) binds to the enzyme, presumably at a cysteine, and there is no turn-over until an external thiol source is available. However, the much less sulfur reactive organnostannanes[15b] do not require such deactivation.

Another feature which is striking is the extraordinary reactivity of all these mercury reagents. While a goal is to elucidate the mechanism of the chemistry occurring as the *O,S*-acetal is broken apart by the mercury reagent bonding to the sulfur, the rates reported in Table IV are consistent with rate-limiting complexation or complex reorganization (Scheme V). For example, in the case of $HgCl_2$ as reagent, the value of 10^6 M^{-1} s^{-1} might arise from either rate-limiting formation of the [complex] or rate-limiting expulsion of Cl$^-$ from the complex to produce {Hg(SEt)Cl} rather than {Hg(SEt)Cl$_2$}$^-$ upon carbon–sulfur bond cleavage. Work is currently underway to elucidate these questions.

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