

oxygen. However, there remains a large difference between cyanolyzed xanthine dehydrogenase and sulfite oxidase. One possible source of this difference is a diminished molybdenum thiolate interaction in xanthine dehydrogenase. Whereas the Mo—S bonds in sulfite oxidase fall at 2.42 Å, a value typical for dioxo dithiolate complexes, the xanthine dehydrogenase Mo—S bond lengths are 0.05 Å longer. Perhaps this decreases the Mo—S interaction and thereby lowers the reduction potential. It is also possible that sulfite oxidase has an extra thiolate ligand in comparison with xanthine dehydrogenase. In any case, it would be useful to have molybdenum thiolate complexes which exhibit these longer Mo—S bonds.

Summary

This work has shown unambiguously that the primary difference between the molybdenum sites of sulfite oxidase and xanthine dehydrogenase is in the nature of the terminal chalcogenides. Some differences in Mo—SR bond lengths were also found. Major changes were always observed upon reduction of the enzymes.

Previous EXAFS results on the molybdenum in nitrogenase^{2,3} prompted a wealth of model-building activity, resulting in the synthesis of Mo,Fe,S clusters with one, two, or three irons bridged by sulfur to molybdenum.⁴³ This has permitted comparison of the properties of model compounds with those of the isolated Fe—Mo cofactor and the intact proteins. An analogous development in mononuclear molybdenum chemistry would certainly be informative. As yet, no mononuclear oxosulfidomolybdenum

complexes have been synthesized, apart from the tetrahedral (MoO_xS_{4-x})²⁻ series. Furthermore, there are no molybdenum thiolate complexes which exhibit the somewhat longer Mo—O bonds (ca. 2.47 ± 0.03 Å) found in xanthine dehydrogenase, although dithiocarbamate complexes with trans effects are known.⁴⁴ Finally, it would be extremely useful to have Mo^{VI}(O)₂ or Mo^{VI}(O)(S) complexes which are stable upon reduction to Mo(V) or Mo(IV) and which exhibit EPR hyperfine splittings similar to those found in the enzymes. The lack of models for the reduced forms in Scheme II may reflect a tendency for such species to dimerize. The synthetic challenges of modeling the active sites of the nonnitrogenase molybdenum enzymes are probably of similar difficulty to those in modeling nitrogenase itself.

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(43) T. E. Wolff, P. P. Power, R. B. Frankel, and R. H. Holm, *J. Am. Chem. Soc.*, **102**, 4694-4703 (1980) and references to other workers therein.

(44) J. M. Berg and K. O. Hodgson, *Inorg. Chem.*, **19**, 2180-2181 (1980).

¹H NMR Rate Constants and Mercury-199 FT NMR Equilibrium Constants Involved in Disulfide Cleavage by Methylmercury

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Abstract: A ¹H NMR kinetic investigation of the cleavage of dimethyl disulfide with methylmercury acetate and triethyl phosphite is described. The metal-assisted —SS— bond rupture is first order in both CH₃Hg^{II} and CH₃SSCH₃. Mercury-199 FT NMR has been employed to measure the equilibrium constants for complexation of CH₃HgOAc with CH₃SSCH₃ and P(OEt)₃. A concomitant electrophilic and nucleophilic mechanism for —SS— bond cleavage is suggested that involves attack by P(OEt)₃ on the —SS— σ* orbital of the CH₃Hg^{II} complex of CH₃SSCH₃.

Few compounds have received the instant notoriety earned by methylmercury after the large scale outbreak of CH₃Hg^{II} poisoning in Minimata Bay, Japan.¹ The realization that alkylmercury derivatives are highly toxic and cause irreversible damage to the central nervous system has stimulated considerable research on the biochemistry and dynamics of methylmercury derivatives.

Our own research efforts have been aimed at elucidating the mechanism of CH₃Hg^{II} migration in living systems by attempting to pinpoint specific targets for CH₃Hg^{II} complexation. After initial ingestion, CH₃Hg^{II} is bound almost exclusively to the sulfhydryl functional group in the cysteine residue of peptides and proteins. The formation constants of a series of methylmercury mercaptides

(CH₃HgSR) range from 10¹⁴ to 10¹⁸, reflecting the thermodynamic stability of sulfur-bound mercury.² Indeed the generic term mercaptan is derived from the Latin *Mercurinum captans* (lit., seizing mercury). The unusually strong covalent bond between mercury and sulfur provides a favored binding site in biological systems. Despite such high formation constants, we have found that mercaptide anion exchange² in RHgSR'—RHgSR'' systems is remarkably fast and provides a potential pathway for migration of organomercurials in nature. The rapid exchange of RS⁻ has been suggested by Rabenstein¹ to be of paramount importance in the biological pathway for alkylmercury migration. Such rapid ligand exchange reactions play a key role in the

(1) For an excellent review, see: Rabenstein, D. L. *Acc. Chem. Res.* **1978**, *11*, 100; *J. Chem. Educ.* **1978**, *55*, 292.

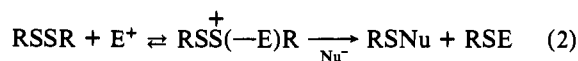
(2) Bach, R. D.; Weibel, A. T. *J. Am. Chem. Soc.* **1976**, *98*, 6241; *Ibid.* **1975**, *97*, 2575.

bioavailability of $\text{CH}_3\text{Hg}^{\text{II}}$ derivatives and prompted us to seek other biological targets for reaction with sulfur-bound $\text{CH}_3\text{Hg}^{\text{II}}$.

Metalloenzymes containing the mercaptide anion should also undergo facile exchange with $\text{CH}_3\text{Hg}^{\text{II}}$. Recently, we established that $\text{CH}_3\text{HgSCH}_2\text{COO}^- \text{K}^+$ reacts quantitatively with the $\text{Fe}_2\text{S}_2(\text{SR})_4$ cluster of adrenodoxin with an activation energy of 17.4 kcal/mol.³ We now extend our mechanistic studies to include the interaction of $\text{CH}_3\text{Hg}^{\text{II}}$ with the disulfide linkage.⁴ The dual objective of this study is to provide kinetic evidence for a metal-assisted concomitant cleavage of the disulfide bond and to establish the role of $\text{CH}_3\text{Hg}^{\text{II}}$ in reactions with this ubiquitous functional group.

Since the disulfide bond of cystine is probably the only covalent cross-linkage in most proteins and peptides, the reaction of the $-\text{SS}-$ moiety with $\text{CH}_3\text{Hg}^{\text{II}}$ could have a profound effect on the tertiary structure of a large variety of natural products. The most commonly encountered electrophiles in $-\text{SS}-$ bond cleavage reactions are H^+ and metal ions with a high affinity for sulfur such as Ag^+ and Hg^{2+} . However, we found no reports of a systematic mechanistic study of metal catalysis of disulfide cleavage.^{5a} Methylmercury iodide has been found to be more effective than HgCl_2 in cleaving the disulfide linkage in wool.^{5b}

Two fundamental pathways must be considered for heterolytic scission of the disulfide bond.^{6,7} The first involves attack at sulfur by a nucleophile with displacement of RS^- (eq 1) and the second results from the combined catalysis of both an electrophile and a nucleophile (eq 2).



Supportive evidence for simple $\text{S}_{\text{N}}2$ displacement at sulfenyl sulfur (eq 1) was provided by Fava in a definitive study involving base-catalyzed isotopic exchange between thiol and disulfide.¹⁰ A second-order rate expression of the form $\text{rate} = k_2[\text{RSSR}][\text{RS}^-]$ was observed. Exchange was also catalyzed by HX ($\text{I}^- > \text{Br}^- > \text{Cl}^-$) but not by highly acidic, but weakly nucleophilic, acids like perchloric acid.^{6a} A series of thorough kinetic studies by Kice on sulfur-sulfur bond rupture have firmly established the concept of an acid-catalyzed concomitant $-\text{SS}-$ bond rupture involving protonation of one sulfur and nucleophilic displacement at the other (eq 2).^{6b,c,11}

Experimental Section

Rate Studies. The ^1H NMR experiments were performed on Varian A-60A and Nicolet 300 MHz spectrometers. The rate of $-\text{SS}-$ bond scission employing the 60-MHz spectrometer was followed by continuously measuring the loss of CH_3SSCH_3 (137 Hz) and the formation of $\text{CH}_3\text{HgSCH}_3$ (136 Hz) in CH_2Cl_2 solution. The above chemical shifts were determined relative to Me_4Si by standard audio frequency sidebanding techniques. The relative $-\text{SCH}_3$ peak areas were measured by

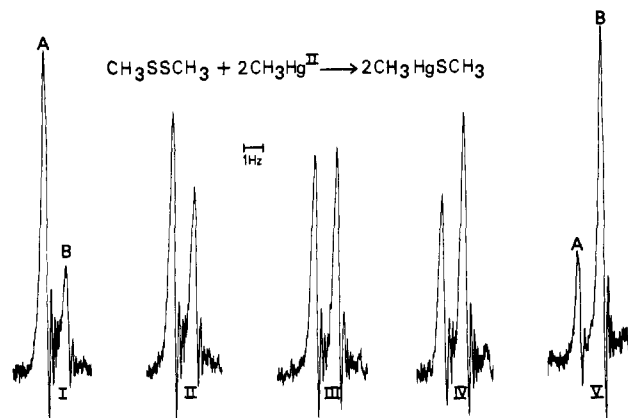


Figure 1. 60-MHz ^1H NMR spectra of the $-\text{SCH}_3$ resonances of CH_3SSCH_3 (A) and $\text{CH}_3\text{HgSCH}_3$ (B) at intermediate stages of disulfide cleavage.

monitoring the intensity of the recorder output signal of the NMR with a Hewlett-Packard Model 3373D electronic integrator using the standard techniques typically employed in gas chromatography. Caution should be exercised to ensure that only a positive voltage is transmitted to the integrator to avoid damage to the circuitry. In addition the output signal was divided (20000:1) by using two resistors (20K Ω and 10 Ω). Two silicon diodes were used to protect the integrator from any input pulse in excess of 0.5 V. The accuracy of the method was checked against standard mixtures of known concentration. The region of the pertinent methyl resonances was rapidly scanned (<50 s) at given time intervals with a minimum of 30 points being recorded for each experiment. The reactions were followed to at least the second half-life. The precision for each experiment is quite reasonable, and the largest source of error is in attaining the same probe temperature for separate experiments.

Experiments with the 300-MHz ^1H NMR were carried out in either CDCl_3 or CH_2Cl_2 solution. The chemical shifts of CH_3SSCH_3 and $\text{CH}_3\text{HgSCH}_3$ were measured to be 727 and 733 Hz in CDCl_3 relative to Me_4Si . However, these relative chemical shifts were reversed in CH_2Cl_2 solvent and found to be 725 and 721 Hz, respectively. The spectra were recorded at 32 specified time intervals that varied from 40 to 120 s depending upon the reaction conditions. The relative areas of the two $-\text{SCH}_3$ signals were integrated at each time interval to determine the changes in concentration with time. We observed excellent agreement between rate studies on both spectrometers.

The CH_3HgOAc was prepared from CH_3HgI and AgOAc and recrystallized twice from ethanol; mp 126.5–127 $^\circ\text{C}$ (lit.¹² 125.5–127.5 $^\circ\text{C}$). Freshly distilled CH_3SSCH_3 and $\text{P}(\text{OEt})_3$ distilled under reduced pressure over sodium metal were added to a 1-mL volumetric flask containing CH_3HgOAc and spectrograde solvent cooled to -15 $^\circ\text{C}$. Measurements were begun as soon as the NMR tube containing the above solution was placed in the probe.

Formation Constant Measurements. The ^{199}Hg spectra were measured by utilizing either the above Nicolet 300 spectrometer or a JEOL JNM-4H-100 spectrometer equipped with a PTF-100 pulse Fourier transform package. With the 100-MHz spectrometer, a fixed frequency fluorine lock at 93.548 603 MHz was utilized. Spectra were measured at a frequency of 17.830 038 MHz, 16- μs pulse width, and a 750-ms preacquisition delay using a 25 000-Hz sweep width. Proton noise decoupling at 99.548 603 MHz center frequency was used. Spectra were measured in 8-mm sample tubes with 10% C_6F_6 by volume as internal fluorine lock. An average of 500 accumulations were taken.

The 300-MHz spectrometer is equipped with a Nicolet 1180 data system using a NTCFT-1180 software package. All spectra were measured at a frequency of 53.712 282 MHz, with a 20- μs pulse width and a 250-ms preacquisition delay using a 35 714.2 Hz sweep width. Data points (8K) were accumulated and zero filled to 32K. A trapezoidal multiplication was used to reduce base line artifacts. An exponential multiplication yielding 15-Hz line broadening was also applied to the free induction decay before Fourier transformation. Ten millimeter sample tubes were used with 50% CDCl_3 or 50% CH_3OD as an internal lock solvent. The spectra represent 4096 scans with ^1H -decoupling frequency of 300.058 421 MHz.

Neat $(\text{CH}_3)_2\text{Hg}$ in a concentric capillary tube was used as an external standard. All ^{199}Hg chemical shifts are reported in parts per million relative to $(\text{CH}_3)_2\text{Hg}$. A negative sign for the chemical shift denotes

(3) Arakawa, S.; Bach, R. D.; Kimura, T. *J. Am. Chem. Soc.* **1980**, *102*, 6847.

(4) A preliminary account of this work has appeared: Bach, R. D.; Rajan, S. J. *J. Am. Chem. Soc.* **1979**, *101*, 3112.

(5) (a) An earlier kinetic study on the reaction of disulfides with silver nitrate did not provide any definitive mechanistic information: Cecil, R.; McPhee, J. R. *Biochem. J.* **1957**, *66*, 538. (b) Leach, S. J. *Aust. J. Chem.* **1960**, *13*, 520, 547.

(6) For reviews see: (a) Ciuffarin, E.; Fava, A. *Prog. Phys. Org. Chem.* **1968**, *6*, 81. (b) Kice, J. L. *Acc. Chem. Res.* **1968**, *1*, 58. (c) Kice, J. L. "Sulfur in Organic and Inorganic Chemistry"; Senning, A., Ed.; Marcel Dekker: New York, 1971; Vol. 1, pp 153–208.

(7) Earlier workers⁸ postulated a third mechanism involving an $\text{S}_{\text{N}}1$ -type cleavage proceeding via an electron-deficient sulfenium ion intermediate (RS^+). There appears to be no unambiguous examples of this mode of reaction, but it has been suggested in two instances.⁹

(8) Benesch, R. E.; Benesch, R. *J. Am. Chem. Soc.* **1958**, *80*, 1666.

(9) (a) Kice, J. L.; Anderson, J. M.; Pawlowski, N. E. *J. Am. Chem. Soc.* **1966**, *88*, 5245. (b) Kice, J. L.; Guaraldi, G. *J. Org. Chem.* **1966**, *31*, 3568.

(10) Fava, A.; Illiceto, A.; Camera, E. *J. Am. Chem. Soc.* **1957**, *79*, 833.

(11) Kice, J. L.; Ekman, G. E. *J. Org. Chem.* **1975**, *40*, 711. (b) Kice, J. L.; Morkved, E. H. *J. Am. Chem. Soc.* **1964**, *86*, 2270.

(12) Scheffold, R. *Helv. Chim. Acta* **1969**, *52*, 56.

Table I. Rate of Cleavage of Dimethyl Disulfide by Methylmercury Acetate in the Presence of Triethyl Phosphite^a

expt	CH ₃ SSCH ₃ , M	CH ₃ HgOAc, M	P(OEt) ₃ , M	temp, °C	10 ⁻⁴ K, s ⁻¹	t _{1/2} , min	% error	corr coeff	NMR freq, MHz
1	0.050	0.500	1.0	15	2.5 ± 0.40	46	3.6	0.987	60
2	0.025	0.500	1.0	15	3.9 ± 0.30	30	4.8	0.990	300
3	0.025	0.250	1.0	5	0.9 ± 0.10	128	3.0	0.960	60
4	0.025	0.250	1.0	5	1.1 ± 0.10	105	4.0	0.981	300
5	0.025	0.250	1.0	15	2.1 ± 0.20	55	2.8	0.990	300
6	0.025	0.250	1.0	26	4.7 ± 0.30	25	1.8	0.994	300
7	0.025	0.250	1.0	35	7.3 ± 0.40	16	2.5	0.993	300
8	0.025	0.250	1.0	20	3.0 ± 0.12	38	2.4	0.996	300

expt	CH ₃ SSCH ₃ , M	CH ₃ HgOAc, M	P(OEt) ₃ , M	temp, °C	10 ⁻² K, mol ⁻¹ s ⁻¹	t _{1/2} , min	% error	corr coeff	NMR freq, MHz
9	0.025	0.050	1.0	43	1.4 ± 0.20	48	3.5	0.993	60
10	0.038	0.070	1.0	43	1.3 ± 0.15	34	3.4	0.989	60
11	0.050	0.100	1.0	43	1.3 ± 0.10	26	2.6	0.995	60
12	0.075	0.150	1.0	43	1.0	21	3.6	0.992	60
13	0.100	0.200	1.0	43	1.1	15	7.3	0.965	60
14	0.050	0.10	1.0	43	1.1 ± 0.10	29	3.3	0.992	300
15	0.050	0.100	0.500	43	0.6 ± 0.05	56	9.0	0.946	300

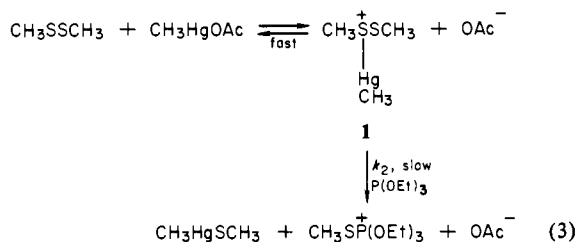
^a Data were collected in CH₂Cl₂ (1, 3, and 9–13) and CDCl₃ (2, 4–8, 14, and 15). The error reported here was obtained from repeating the same experiment three to seven times. The percent error is based upon the average of the standard deviations of the least-square plots.

resonances to higher field or lower frequency. No bulk susceptibility corrections were made.

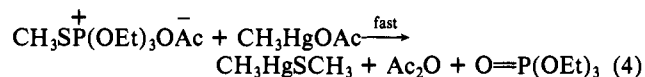
Results

Kinetics of Disulfide Bond Cleavage. There are relatively few analytical methods available that afford reliable rate measurements for the cleavage of the –SS– bond. We chose dimethyl disulfide as our model substrate because of solubility and the simplicity of its NMR spectrum. However, when CH₃HgOAc was used as the electrophile, the methyl resonance of the reactant CH₃SSCH₃ and product CH₃HgSCH₃ was separated by only 1 Hz. This problem was circumvented by utilizing an electronic integrator employing methodology for measuring peak areas in gas chromatography (*vide supra*). With this modification we realized our first objective in this study and were able to determine the rate of cleavage of CH₃SSCH₃ by the combined action of the electrophile CH₃HgOAc and the nucleophile P(OEt)₃.

The rate of –SS– bond scission was followed in the NMR by measuring the loss of CH₃SSCH₃ and the formation of CH₃HgSCH₃ (eq 3). A second mole of CH₃Hg⁺ is consumed in a



subsequent rapid reaction (eq 4). Our first series of experiments



utilizing the 60-MHz spectrometer are illustrated in Figure 1 where five intermediate stages of reaction are shown. In these spectra resonance A is for the dimethyl disulfide.

Since the minimal peak separation of 1 Hz at 60 MHz severely tested the limits of that instrument, we extended our study to include kinetic measurements taken at 300 MHz where the two pertinent methyl resonances are separated by 6 Hz. The NMR spectra for six data points are given in Figure 2 where signal B is the –SCH₃ resonance of the product CH₃HgSCH₃. In these spectra signal B is downfield from A as a result of a shift in relative resonance frequency due to the change in solvent from CH₂Cl₂ to CDCl₃. The results from both spectrometers are summarized in Table I, where rate constants measured under both pseudo-first- and pseudo-second-order conditions are given.

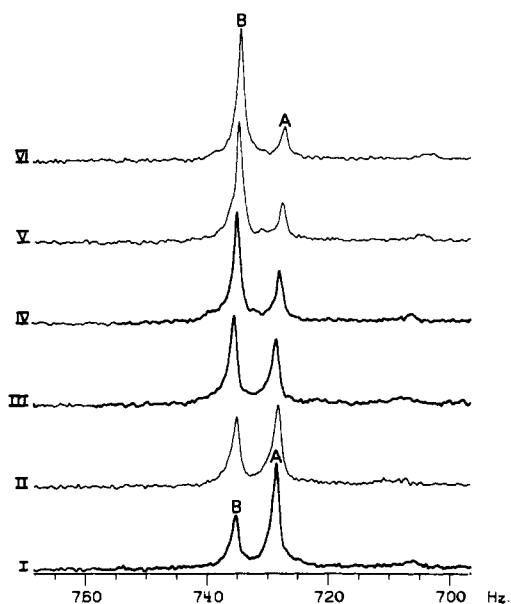
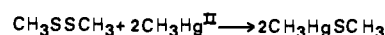


Figure 2. 300-MHz ¹H NMR spectra of the –SCH₃ resonances of CH₃SSCH₃ (A) and CH₃HgSCH₃ (B) at intermediate stages of disulfide cleavage.

The pseudo-first-order data, where the rate is $k_1[\text{CH}_3\text{SSCH}_3]$, was measured while maintaining an excess of both CH₃HgOAc and P(OEt)₃. The rate constants were determined by using the rate expression $\ln[(C_1 + C/C_1) = k_1t]$, where C₁ is the integrated area for the methyl resonances of CH₃SSCH₃ and C represents the area for the methyl mercaptide protons in CH₃HgSCH₃. All plots were linear, and the correlation coefficients along with the other data are also given in Table I. The rate constants $k_1 = 2.5$ (±0.4) and 2.1 (±0.2) × 10⁻⁴ s⁻¹ were observed with 60- and 300-MHz spectrometers, respectively. In both experiments a 10:1 molar ratio of CH₃HgOAc to CH₃SSCH₃ was employed at 15 °C. The rate constant approximately doubled when this molar ratio was increased to 20:1 (experiment 2). The P(OEt)₃ concentration was held constant at 1.0 M which is at least a 20-fold excess relative to the limiting reagent.

The thermodynamic parameters for CH₃SSCH₃ cleavage were obtained by measuring the rate at five different temperatures. Linear least-squares analysis of these data gave a correlation coefficient of 0.99 with $\Delta H^\ddagger = 10.61$ kcal/mol, $\Delta S^\ddagger = -37.86$ eu,

and $\Delta G^\ddagger = 21.9$ kcal/mol at 25 °C. The high negative entropy of activation is consistent with the proposed mechanism involving bimolecular displacement by $\text{P}(\text{OEt})_3$ on the sulfonium ion intermediate **1** (eq 3).

Second-order kinetic behavior was demonstrated at several different concentrations of reactants. The rate of $-\text{SS}-$ cleavage is given by $k_{\text{obsd}}[\text{CH}_3\text{SSCH}_3][\text{CH}_3\text{HgOAc}]$. Actually $k_{\text{obsd}} = K_{\text{eq}} 2k_2[\text{P}(\text{OEt})_3]$ where K_{eq} is the equilibrium constant for the formation of sulfonium ion **1** (eq 3). Consistent with this rate expression, the rate constant k_{obsd} is seen to diminish by about half when the $\text{P}(\text{OEt})_3$ concentration was reduced to 0.5 M (experiment 15). The rate constants were obtained from the expression $(C/C_1)(1/a) = k_{\text{obsd}}t$ where a is the initial concentration of CH_3SSCH_3 . A plot of the half-lives calculated for the initial concentrations vs. $1/a$ afforded, as the reciprocal of the slope,¹³ the rate constant $k_{\text{obsd}} = 1.24 \times 10^{-2} \text{ mol}^{-1} \text{ s}^{-1}$.

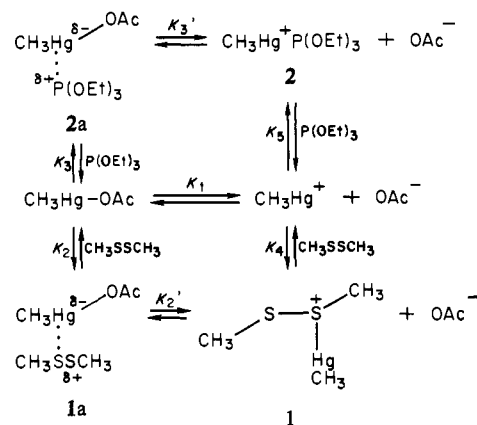
Control experiments have established that neither CH_3HgOAc (24 h) nor $\text{P}(\text{OEt})_3$ (48 h) at temperatures as high as 50 °C will effect $-\text{SS}-$ bond cleavage. In addition, CH_3SSCH_3 itself is not competing with $\text{P}(\text{OEt})_3$ as the effective nucleophile at temperatures up to 80 °C. Triethyl phosphite will, however, cleave a dialkyl disulfide at elevated temperatures.¹⁴ In our preliminary studies we found that hydroxide ion and secondary amines could also serve as the nucleophile in this reaction but their use was complicated by secondary reactions that gave nonlinear kinetic plots. We also found that highly ionic mercurials such as CH_3HgNO_3 , in the absence of added nucleophile, or highly associated ones like CH_3HgI , where the concentration of CH_3Hg^+ is minimal, fail to catalyze $-\text{SS}-$ bond scission.

In support of the proposed second rapid step in this cleavage process (eq 4), we have isolated acetic anhydride, triethyl phosphate, and $\text{CH}_3\text{HgSC}_6\text{H}_5$ (75%) from the reaction mixture of the comparable cleavage of diphenyl disulfide. NMR experiments have also established that an alkylmercury mercaptide (RHgSR') is incapable of achieving $-\text{SS}-$ bond rupture. We observed no significant change in CH_3SSCH_3 concentration in the presence of 10 equiv of $\text{CH}_3\text{HgSC}_6\text{H}_5$ and 20 equiv of $\text{P}(\text{OEt})_3$ after 22 h. This is a particularly significant result since most of the $\text{CH}_3\text{Hg}^{\text{II}}$ in living systems is bound to sulfur and *RHgSR* compounds should therefore not be involved in disulfide cleavage reactions.

Formation Constant Measurements. Our kinetic studies on dimethyl disulfide are consistent with the simultaneous involvement of both $\text{CH}_3\text{Hg}^{\text{II}}$ and $\text{P}(\text{OEt})_3$ in a "concomitant cleavage" step. Implicit in this mechanism is the rapid reversible formation of sulfonium ion **1** (eq 3). Any definitive mechanistic study of this cleavage reaction must address itself to the identity of the actual electrophilic species in solution. Since the $\text{CH}_3\text{Hg}^{\text{II}}$ can be associated with acetate ion, disulfide, or phosphite, the relative concentrations of the possible ionic species present in such a complex mixture presents a challenging problem. Although mercury typically exhibits a high affinity for sulfur in the form of its mercaptide anion ($K_{\text{stab}} \approx 10^{16}$), there is no data available concerning the positions of equilibria between $\text{CH}_3\text{Hg}^{\text{II}}$ and $-\text{SS}-$ or $\text{P}(\text{OR})_3$. In the interest of rigor we sought to establish the magnitude of the equilibrium constants that comprise the observed rate constants ($k_{\text{obsd}} = K_{\text{eq}}k_2[\text{P}(\text{OEt})_3]$).

The equilibrium processes most fundamental to our proposed mechanism are given in Scheme I. Examination of these multiple equilibria points to the overall complexity of this reaction. However, the problem of measuring the K_{eq} for $\text{CH}_3\text{Hg}^{\text{II}}$ complexation can be greatly simplified by assuming that all processes involving CH_3Hg^+ will be relatively unimportant in CH_2Cl_2 solvent and that K_4 and K_5 can be neglected. This would appear to be a valid approximation since CH_3HgOAc is not highly dissociated and its K_{stab} is at least $10^{3.3}$ in CH_2Cl_2 solvent.² At a CH_3HgOAc concentration of 0.25 M the concentration of CH_3Hg^+ could not

Scheme I



be greater than 0.01 M. The problem that remains is to assess the relative concentrations of sulfonium ion **1** and the phosphite complex **2** derived from ionization of the initial complexes **1a** and **2a**, respectively (Scheme I). We therefore assumed that the total concentration of $\text{CH}_3\text{Hg}^{\text{II}}$ at equilibrium is represented by eq 5,

$$\text{CH}_3\text{Hg}_{\text{total}}^{\text{II}} = \text{CH}_3\text{Hg}_t^{\text{II}} + \text{CH}_3\text{Hg}_t^{\text{II}}\text{CH}_3\text{SSCH}_3 + \text{CH}_3\text{Hg}_t^{\text{II}}\text{P}(\text{OEt})_3 \quad (5)$$

where $\text{CH}_3\text{Hg}_t^{\text{II}} = \text{CH}_3\text{HgOAc} + \text{CH}_3\text{Hg}^+$, the concentration of $\text{CH}_3\text{Hg}^{\text{II}}$ species with and without an acetate anion in its primary solvent shell.

The three pertinent equilibria involved are therefore

$$K_1 = [\text{ML}_1]/([\text{M}][\text{L}_1]) \quad K_2 = [\text{M}_t\text{L}_2]/([\text{M}_t][\text{L}_2]) \\ K_3 = [\text{M}_t\text{L}_3]/([\text{M}_t][\text{L}_3])$$

where $\text{M} = \text{CH}_3\text{Hg}^+$, $\text{M}_t = \text{CH}_3\text{Hg}_t^{\text{II}}$, $\text{L}_1 = \text{OAc}^-$, $\text{L}_2 = \text{CH}_3\text{SSCH}_3$, and $\text{L}_3 = \text{P}(\text{OEt})_3$. Substitution of these expressions into eq 5 gives eq 6–9, the relative population of the metal species in

$$[\text{M}_T] = [\text{ML}_1] \left(\frac{1}{K_1[\text{L}_1] + 1} \right) (1 + K_1[\text{L}_1] + K_3[\text{L}_3]) \quad (6)$$

$$[\text{ML}_1] = \frac{\text{M}_T}{(1 + 1/(K_1[\text{L}_1]))(1 + K_2[\text{L}_2] + K_3[\text{L}_3])} \quad (7)$$

$$[\text{M}_T\text{L}_2] = [\text{ML}_1] \left(1 + \frac{1}{K_1[\text{L}_1]} \right) K_2[\text{L}_2] \quad (8)$$

$$[\text{M}_T\text{L}_3] = [\text{ML}_1] \left(1 + \frac{1}{K_1[\text{L}_1]} \right) (K_3[\text{L}_3]) \quad (9)$$

solution at equilibrium. It can be seen from eq 8 and 9 that the relative concentrations of complex **1a** and **2a** will be determined by the ratio $K_2[\text{L}_2]/K_3[\text{L}_3]$.

In preliminary experiments aimed at measuring the magnitude of K_2 and K_3 , we examined the ^1H NMR spectrum of a solution (CH_2Cl_2) of CH_3HgOAc in the presence of excess CH_3SSCH_3 . We observed no measurable change in proton chemical shift or $J(^{199}\text{Hg}-^1\text{H})$ coupling constant with up to 10 equiv of disulfide at 60 MHz. However, we did see a modest decrease in the $J(^{199}\text{Hg}-^1\text{H})$ coupling constant (212–206 Hz) of CH_3HgOAc in the presence of 10 equiv of $\text{P}(\text{OEt})_3$. This is not a significant change since this coupling constant is 156 Hz with a highly covalent mercurial like $\text{CH}_3\text{HgSCH}_3$.² Similarly, the change in ^{13}C chemical shift was not sufficiently sensitive to the environment of $\text{CH}_3\text{Hg}^{\text{II}}$ to provide a quantitative measure of these equilibrium constants. Even in the presence of 10 equiv of CH_3SSCH_3 or $\text{P}(\text{OEt})_3$ the ^{13}C chemical shift of the methyl resonance of CH_3HgOAc was shifted by only 0.05 and 0.5 ppm, respectively. The ^{13}C chemical shift of CH_3SSCH_3 was also essentially invariant to the presence of CH_3HgOAc .

We next turned our attention to Raman spectroscopy where we attempted to correlate the shift of the symmetrical $-\text{SS}-$

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Table II. K_f and δ_x Values for $\text{CH}_3\text{HgX} + \text{L} \rightleftharpoons \text{CH}_3\text{Hg}^+\text{XL}^-$ (K_f)

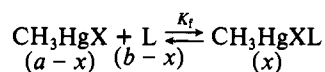
expt	X	L	solvent	[MeHgX], mol/L	δ_0	$\delta_x - \delta_0^a$	K_f				NMR freq, MHz
							eq 13	eq 14	eq 15	eq 16	
16	OAc	CH_3SSCH_3	CH_2Cl_2	0.15	-1080.72	111	0.07 91	0.06 101	0.05 116	0.04 ^f 135 ^g	100
17	OAc	CH_3SSCH_3	CH_2Cl_2	0.15	-1091.50	105	0.06 102	0.05 107	0.05 106	0.05 106	300
18	OAc	CH_3SSCH_3	CH_2Cl_2	0.25	-1082.43	89	0.07 83	0.06 93	0.06 90	0.07 89	100
19	OAc	CH_3SSCH_3	CH_2Cl_2	0.35	-1083.80	150	0.06 97	0.06 99	0.03 ^f 202	0.03 ^f 201	100
20	OAc	CH_3SSCH_3	MeOH	0.15	-1133.33	60	1.00 59	1.00 59	0.89 61	0.98 60	300
21	OC(=O)CF_3	CH_3SSCH_3	CH_2Cl_2	0.15	-1140.13	369	0.09 273	0.05 451	0.06 374	0.06 377	100
22	OAc	P(OEt)_3	CH_2Cl_2	0.15	-1081.94	244	0.66 243	0.66 242	0.59 249	0.66 240	100
23	OAc	P(OEt)_3	CH_2Cl_2	0.25	-1082.43	259	0.47 256	0.47 256	0.41 267	0.47 256	100
24	OAc	$(n\text{-Bu})_2\text{S}$	CH_2Cl_2	0.15	-1090.50	368	0.04 363	0.03 456	0.04 330	0.04 324	100
25	Cl^b	Cl^-	EtOH	0.10	-899.16 ^{b,d}	167	0.28 172	0.30 160	0.28 170	0.29 166	100
26	Br^b	Br^-	EtOH	0.06	-938.51 ^{b,d}	141	1.08 140	0.99 146	1.05 138	1.08 140	100
27	OAc	PhSSCH_3	CH_2Cl_2	0.15	-1090.52	116	0.06 105	0.07 87	0.04 ^f 147	0.05 ^f 125	300
28	OAc	$(\text{Ph})_2\text{S}^c$	CH_2Cl_2	0.25	-1082.43 ^e						100
29	OAc	PhSSPh^c	CH_2Cl_2	0.25	-1082.43 ^e						100
30	SCH_3	$\text{CH}_3\text{SSCH}_3^c$	CH_2Cl_2	0.25	-484.72 ^e						100

^a Average. ^b Reference 19a. ^c Equilibrium constant too small to measure. ^d Calculated. ^e $\delta_x - \delta_0$ in range of 0.5–4 ppm. ^f The standard deviation was high. ^g Values under K_f are the calculated $\delta_x - \delta_0$ for each equation.

stretching frequency upon complexation with CH_3HgOAc . Skeletal Raman frequencies of $[\text{CH}_3\text{HgS}(\text{CH}_3)_2]\text{NO}_3$ have been reported.¹⁵ However, we noted no discernible change in the 518-cm^{-1} band of CH_3SSCH_3 in CH_2Cl_2 upon addition of 1 equiv of CH_3HgOAc . It was therefore obvious that we needed a much more sensitive analytical probe to effectively measure the extent of aggregation of CH_3HgOAc under our reaction conditions.

The unusual sensitivity of the ^{199}Hg nucleus to its immediate environment is reflected in a range of chemical shift differences that span over 4000 ppm for a series of organic and inorganic mercury compounds.¹⁶ The large chemical shift of mercury can be rationalized by theories developed by Ramsey,¹⁷ Slichter,^{18a} and others.^{18b,c} There have been several recent reports where ^{199}Hg FT NMR has been employed to measure halide complexation with alkylmercury(II) halides¹⁹ and aqueous complexes of methylmercury cation.²⁰

We found that the formation constants, K_f , which we sought could also be measured by a least-squares fit of ^{199}Hg NMR data. For the equilibrium attained by the interaction of CH_3HgX with added ligand L, it follows that



if one assumes no prior dissociation or association of the reactants. If the initial concentration of CH_3HgX (a) is held constant and the concentration of ligand is b , then the equilibrium molar

concentration of complex x may be expressed in terms of (x/a) , the molar ratio of complex to initial concentration of CH_3HgX (eq 10). Since equilibrium is attained rapidly on the NMR time

$$K_f = \frac{x}{(a-x)(b-x)} = \frac{x/a}{(1-x/a)(b/a-x/a)} \quad (10)$$

scale, only one mercury resonance is observed. With the chemical shift varies linearly with added ligand, the observed shift in ^{199}Hg resonance frequency as a result of complexation, $\Delta\delta$, will result from a weighted average of the mole fraction of CH_3HgX ($(a-x)/a$) with frequency δ_0 and the complexed mercurial CH_3HgXL (x/a) having a chemical shift δ_x (eq 11). Since the

$$\Delta\delta + \delta_0 = \delta_0 \left(\frac{a-x}{a} \right) + \delta_x \left(\frac{x}{a} \right) = \delta_{\text{obsd}} \quad (11)$$

sum of the above mole fractions equals one, it follows from eq 11 that $(x/a) = \Delta\delta / (\delta_x - \delta_0)$ which upon substitution into eq 10 may be expressed as the following quadratic equation (eq 12).

$$\left(\frac{\Delta\delta}{\delta_x - \delta_0} \right)^2 - \frac{a+b+K_f^{-1}}{a} \left(\frac{\Delta\delta}{\delta_x - \delta_0} \right) + \frac{b}{a} = 0 \quad (12)$$

Having derived this general expression, it now remained to express the observable change in chemical shift, $\Delta\delta$, a measurable quantity, in terms of the initial concentration of reactants and the two parameters $\delta_x - \delta_0$ (a constant) and the desired K_f as a manageable quadratic expression (eq 13), where $\alpha_1 = \delta_x - \delta_0$ and

$$\Delta\delta = \frac{1}{a} \left[\left(\left(\frac{a+b}{2} \right) \alpha_1 + \frac{\alpha_2}{2} \right) - \sqrt{\left(\frac{a+b}{2} \alpha_1 + \frac{\alpha_2}{2} \right)^2 - ab\alpha_1^2} \right] \quad (13)$$

$\alpha_2 = K_f^{-1}(\delta_x - \delta_0)$. The procedure employed in evaluation of eq 13 is to substitute the experimental parameters $\Delta\delta$, δ_0 , a , and b and vary the two adjustable parameters K_f and δ_x until the calculated chemical shifts correspond to the experimental $\Delta\delta$ values within the error limits on the concentration of a and b (0.01 M) and the chemical shifts (0.05 ppm). The experimental data were

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Table III. ^{199}Hg Chemical Shifts for CH_3HgX in Methylene Chloride with Added Ligand

[ligand], mol/L	[L]/[MeHgX]	chem shift, ppm	$\Delta\delta$, ppm
MeHgOAc + dimethyl disulfide			
0.00	0.00	-1082.43	0.00
1.27	5.08	-1076.25	6.19
1.53	6.12	-1074.22	8.22
1.78	7.12	-1073.51	8.93
2.03	8.01	-1072.14	10.30
2.30	9.20	-1070.77	11.67
2.54	10.16	-1070.11	12.32
2.80	11.20	-1069.40	13.04
3.05	12.20	-1068.03	14.41
MeHgOCOCF ₃ + dimethyl disulfide			
0.00	0.00	-1133.75	00.00
1.00	4.00	-1112.56	21.19
1.20	4.80	-1109.11	24.64
1.40	5.60	-1105.71	28.04
1.60	6.40	-1102.64	31.11
1.80	7.20	-1098.87	34.88
2.00	8.00	-1096.13	37.62
2.20	8.80	-1093.06	40.69
2.40	9.60	-1089.94	43.81
MeHgOAc + triethyl phosphite			
0.00	0.00	-1082.43	00.00
0.75	3.00	-1017.37	65.07
1.00	4.00	-1003.02	79.42
1.50	6.00	-982.48	99.96
1.75	7.00	-970.15	112.28
2.00	8.00	-961.94	120.50
2.25	9.00	-960.57	121.87
2.50	10.00	-950.27	132.16
MeHgOAc + di- <i>n</i> -butyl sulfide			
0.00	0.00	-1090.21	0.00
0.30	2.00	-1086.02	4.19
0.38	2.50	-1084.96	5.25
0.45	3.00	-1084.08	6.13
0.53	3.50	-1083.08	7.13
0.60	4.00	-1082.05	8.16
0.75	5.00	-1080.02	10.19
0.90	6.00	-1077.80	12.41
1.05	7.00	-1075.82	14.39
1.20	8.00	-1074.19	16.02
1.35	9.00	-1072.17	18.04
1.50	10.00	-1070.49	19.72
MeHgOAc + thiophenol			
0.000	0.00	-1082.43	00.00
0.025	0.10	-1036.21	46.22
0.050	0.20	-983.52	98.81
0.075	0.30	-932.11	150.32
0.100	0.40	-881.47	200.96
0.125	0.50	-834.53	247.90
0.150	0.60	-771.54	310.89
0.175	0.70	-729.48	352.95
0.200	0.80	-686.69	395.95
0.225	0.90	-632.96	449.47
0.250	1.00	-578.52	503.91
0.275	1.10	-578.52	503.91
0.300	1.20	-578.78	503.65

analyzed on an Amdahl 470V/6 computer using the general nonlinear curve fitting program KINFIT⁴¹ with appropriate equations described herein. A series of typical experiments are given in Table III. Each experiment was carried out in triplicate, and the K_f and δ_x values in Table II were calculated from a least-squares analysis of several combined data sets.

The validity of this approach to the measurements of formation constants has been amply demonstrated by Popov and his co-workers.²² In an extensive series of papers they have measured

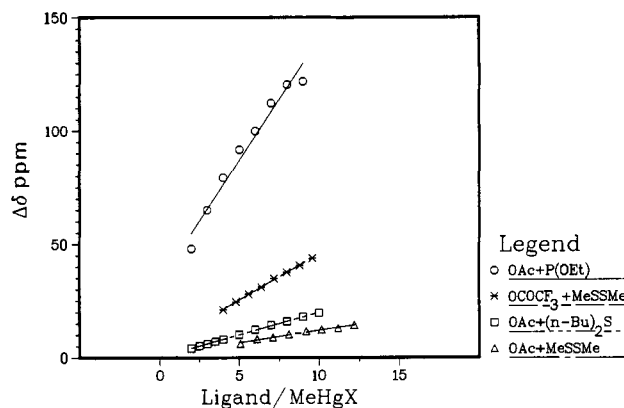


Figure 3. Plot of ^{199}Hg chemical shifts vs. molar ratios of ligand/MeHgX.

the formation constants for the complexation of alkali metals with cryptates in various solvents.²³ An expression comparable to eq 13 has been derived by Popov (eq 14)²⁴ in terms of $((a-x)/a)$

$$\delta_0 + \Delta\delta = \frac{[-K_f(b-a) - 1 + \sqrt{[K_f(b-a) + 1]^2 + 4aK_f}] (\delta_0 - \delta_x) + \delta_x}{2aK_f} \quad (14)$$

instead of (x/a) as in eq 11. We elected to use the molar ratio of complex to free $\text{CH}_3\text{Hg}^{\text{II}}(x/a)$ since in the present study the methylmercury is weakly complexed; i.e., K_2 and K_3 are both relatively small.

With use of either eq 13 or 14, δ_x , the chemical shift of the complexed metal a can be determined experimentally for a relatively strong complex if such an excess of ligand b is added that essentially all of the free metal having chemical shift (δ_0) is in its complexed form. However, for the relatively weak complexes **1a** and **2a**, the limiting chemical shift δ_x was not directly attainable experimentally but was evaluated by using the above equations. A comparison of these calculated adjustable parameters K_f and δ_x is given in Table II. Linear plots of ^{199}Hg chemical shifts vs. ligand/ CH_3HgX ratios are given in Figure 3.

When relatively weak complexes are involved, a large excess of ligand is required which potentially has the disadvantage of effecting deviation from ideal solution behavior. However, the change in chemical shift is typically linear with respect to added ligand when K_f is small. A linear expression has been derived from eq 11 by Lucchini and Wells^{19a} that simplifies analysis of the data. If conditions are such that $b \gg a$ and/or K_f is very small, then the reciprocal of the ligand-induced changes in chemical shift, $\Delta\delta^{-1}$, is linearly related to the reciprocal of the ligand concentration, b^{-1} , at constant metal concentration a such that

$$\Delta\delta^{-1} = K_f^{-1}(\delta_x - \delta_0)^{-1}b^{-1} + (\delta_x - \delta_0)^{-1} \quad (15)$$

The validity of this approximation has been established by a comparison of the equilibrium constants evaluated from eq 16, where the above constraints have been removed and both a and b may be varied and where $\beta_1 = (\delta_x - \delta_0)^{-1}$ and $\beta_2 = K_f^{-1}(\delta_x - \delta_0)^{-1}$.

$$\Delta\delta^{-1} = \frac{1}{b} \left[\left(\frac{a+b}{2}\beta_1 + \frac{\beta_2}{2} \right) + \sqrt{\left(\frac{a+b}{2}\beta_1 + \frac{\beta_2}{2} \right)^2 - ab\beta_1^2} \right] \quad (16)$$

The dramatic changes in the chemical shift of the ^{199}Hg resonance of CH_3HgX upon complexation with added ligands are

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evident from the data given in Table III. It is instructive to compare the relative values of ($\Delta\delta$) upon addition of 8 equiv of ligand to 0.25 M solutions of CH_3HgX in CH_2Cl_2 . With the weakly bound CH_3SSCH_3 , CH_3HgOAc exhibits a ($\Delta\delta$) = 10.3 ppm ($K_f = 0.06$). The more ionic methylmercury trifluoroacetate allows the ligand to compete more favorably with X and ($\Delta\delta$) = 37.6 ppm with an attendant increase in K_f to 0.08. With highly covalent mercurials like $\text{CH}_3\text{HgSCH}_3$ (experiment 29), the K_f for complexation with a disulfide is too small to measure. The higher donicity of $\text{P}(\text{OEt})_3$ is reflected in a $\Delta\delta = 120.5$ ppm with a calculated value for K_f of 0.47 with CH_3HgOAc . It may also be seen that alkyl groups increase the donor ability of a disulfide and aryl groups markedly diminish its Lewis basicity. Thus, the change in chemical shift for diphenyl disulfide was too small to measure accurately. Although di-*n*-butyl sulfide has a $\Delta\delta = 16.0$ ppm, its K_f is slightly lower (experiment 24) than that of dimethyl disulfide.

The most striking change in chemical shift was observed upon addition of PhSH to CH_3HgOAc . With a [ligand]/ $[\text{CH}_3\text{HgOAc}]$ ratio of only 1.0, a $\Delta\delta$ of 503.9 ppm was observed which reflects the high K_{stab} ($\sim 10^{16}$) for formation of CH_3HgSPh . When the K_f is high and the concentration of donor is such that essentially all of the acceptor is complexed, then further addition of donor does not change the chemical shift in the absence of solvent polarity effects. In the present case an increase in ligand concentration above a 1:1 ratio did not result in further change in $\Delta\delta$ since the limiting value of $\delta_x - \delta_0$ had been attained. It should therefore be emphasized that the present method for measuring equilibrium constants is not accurate when K_f is greater than 10^4 – 10^5 since measurable concentrations of free metal are not present in solution.

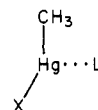
In those cases where the stability constant is quite low, the increase in $\Delta\delta$ with ligand concentration is typically small but linear. However, it is experimentally difficult to get the concentration of complex high enough such that a linear plot of the data (using eq 15) has an intercept that is significantly different from zero.²⁵ This introduces a considerable error in the calculation of K_f from the slope, $K_f^{-1}(\delta_x - \delta_0)^{-1}$. A second problem encountered with small values of K_f is that the magnitude of $\Delta\delta$ can be significantly influenced by a change in solvent polarity¹⁶ when high concentrations of ligand are required to affect a measurable quantity of complex. For example, addition of 10 equiv of the relatively polar ($\epsilon = 24.5$) but weakly nucleophilic compound ethanol to a 0.15 solution of CH_3HgOAc gave a chemical shift of -1099.59 ppm which is shifted 9.4 ppm from δ_0 in the opposite direction to that observed with CH_3SSCH_3 and $\text{P}(\text{OEt})_3$ ($\epsilon = 2.4$).²⁶ We further emphasize that in those cases where the solvent-induced chemical shift is in the opposite direction to that observed upon metal complexation, the calculated K_f may actually be erroneously diminished. There is also a small concentration effect on the ^{199}Hg resonance. When the CH_3HgOAc concentration is varied from 0.15 to 0.35 M, δ_0 exhibits a chemical shift difference of 2.1 ppm to higher field. However, the measured K_f at these concentrations remain essentially constant (experiments 16 and 19) within experimental error. As anticipated the K_f increases markedly on going from CH_2Cl_2 solvent to the more polar CH_3OH where the dissociation of CH_3HgOAc (K_1) is enhanced. However, with charged ligands such as Cl^- or Br^- (experiments 25 and 26)^{19a} an increase in solvent polarity impedes complexation as a result of solvation of the halide ions.^{19b} This behavior is quite analogous to that observed in $\text{S}_{\text{N}}2$ displacement reactions at saturated carbon.

It is the region between the extremes of very high and low K_f where the present method of measuring equilibrium constants should prove most useful. In those cases where the metal is moderately complexed but yet a plot of $\Delta\delta$ vs. $[\text{L}]/[\text{CH}_3\text{HgX}]$ is linear as in Figure 3, the linear expression given in eq 15 should

be adequate. However, when K_f is ~ 5 or greater the nonlinear quadratic expressions given in eq 13, 14, and 16 are recommended. The agreement between all four methods of calculation of K_f shown in Table II is gratifying when one considers the basic differences in these equations ((13)–(16)). We have less confidence in the calculated values of δ_x since it is very difficult to accurately extrapolate to the chemical shift of the fully complexed metal especially when K_f is small. Our calculated equilibrium constants for complexation of chloride ion with CH_3HgCl are in good agreement with those reported by Lucchini and Wells.^{19a}

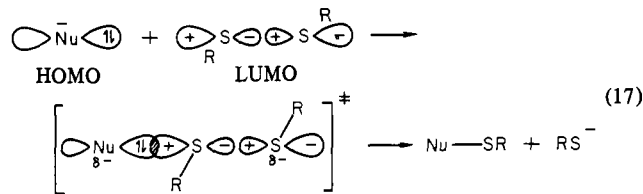
Discussion

The combined kinetic and thermodynamic studies described above fully support the overall concomitant mechanism for disulfide cleavage given in eq 3 and 4. The rate data clearly implicate $\text{CH}_3\text{Hg}^{\text{II}}$ in the rate-limiting step. Our suggestion of rapid reversible formation of sulfonium ion **1** by complexation of CH_3HgOAc with CH_3SSCH_3 is consistent with the surprisingly low $K_f = 0.06$ that we have measured. Although most of the $\text{CH}_3\text{Hg}^{\text{II}}$ is present as its $\text{P}(\text{OEt})_3$ complex, it can be estimated from eq 7 that CH_3HgOAc is present in solution. However, the mechanism of the cleavage step is independent of the actual ionic precursor to the required sulfonium ion **1**. It is only necessary that a finite concentration of **1** be in solution in the presence of free $\text{P}(\text{OEt})_3$. Based upon vibrational and NMR studies, Goggin^{19b} has suggested that the initial complexes of CH_3HgX with an added ligand have an essentially linear RHgX group with the ligand L much more weakly attached in the equatorial plane as depicted.



We suggest a similar behavior in Scheme I, where complex **1a** dissociates to sulfonium ion **1** prior to nucleophilic attack by $\text{P}(\text{OEt})_3$ (eq 3). Implicit in this suggestion is the fact that K_2' is not making a large contribution to the observed chemical shift.

The suggested mechanism may also be rationalized on the basis of fundamental theoretical considerations. Frontier orbital theory suggests that nucleophilic $-\text{SS}-$ bond cleavage (eq 1) proceeds by attack of the lone pair of the nucleophile (HOMO) on the empty σ^* orbital of the disulfide bond (LUMO). Transfer of electron density from the nucleophile to the antibonding σ^* MO will induce $-\text{SS}-$ bond rupture and displacement of RS^- (eq 17).



The displacement of RS^- is, in principle, comparable with a typical $\text{S}_{\text{N}}2$ displacement at saturated carbon, and by analogy, there is no need to invoke a negatively charged intermediate or d orbital participation for the $-\text{SS}-$ bond breakage. Indeed, a recent search for a kinetically distinguishable metastable intermediate in the reaction of thiols with Ellman's reagent proved futile.^{28a} More recently Whitesides has provided kinetic evidence that supports a simple $\text{S}_{\text{N}}2$ pathway for disulfide exchange reactions with thiolate anions.^{28b} Similarly Overman has shown that cleavage of the $-\text{SS}-$ bond by Ph_3P is rate limiting.^{28c} In a particularly interesting report by Kice,²⁹ it was suggested that nucleophilic displacement at sulfonyl sulfur is at least 10^9 – 10^{10} faster than displacement at sp^3 carbon, thereby reflecting the relatively low (~ 42 kcal/mol) sulfur–sulfur bond energy.³⁰

(25) For a discussion of a reliability criterion for formation constants of weak complexes see: Person, W. B. *J. Am. Chem. Soc.* **1965**, *87*, 167.

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