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

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Abstract: A ^{1}H 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 CH_3Hg^{II} and CH_3SSCH_3. Mercury-199 FT NMR has been employed to measure the equilibrium constants for complexation of CH_3HgOAc with CH_3SSCH_3 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 CH_3Hg^{II} complex of CH_3SSCH_3.

Few compounds have received the instant notoriety earned by methylmercury after the large scale outbreak of CH_3Hg^{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 CH_3Hg^{II} migration in living systems by attempting to pinpoint specific targets for CH_3Hg^{II} complexation. After initial ingestion, CH_3Hg^{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 (CH_3HgSR) range from 10^{14} to 10^{18}, reflecting the thermodynamic stability of sulfur-bound mercury.[2] Indeed the generic term mercaptan is derived from the Latin *Mercurinium 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 exchange[2] 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 Rabenstein[1] to be of paramount importance in the biological pathway for alkylmercury migration. Such rapid ligand exchange reactions play a key role in the

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bioavailability of CH_3Hg^{II} derivatives and prompted us to seek other biological targets for reaction with sulfur-bound CH_3Hg^{II}.

Metalloenzymes containing the mercaptide anion should also undergo facile exchange with CH_3Hg^{II}. Recently, we established that $CH_3HgSCH_2COO^-K^+$ reacts quantitatively with the $Fe_2S_2(SR_4)$ cluster of adrenodoxin with an activation energy of 17.4 kcal/mol.[3] We now extend our mechanistic studies to include the interaction of CH_3Hg^{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 CH_3Hg^{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 –SS– moiety with CH_3Hg^{II} could have a profound effect on the tertiary structure of a large variety of natural products. The most commonly encountered electrophiles in –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).

$$RSSR + Nu^- \rightarrow RSNu + RS^- \quad (1)$$

$$RSSR + E^+ \rightleftarrows RS\overset{+}{S}(\text{—}E)R \xrightarrow[Nu^-]{} RSNu + RSE \quad (2)$$

Supportive evidence for simple S_N2 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 rate = k_2[RSSR][RS^-] was observed. Exchange was also catalyzed by HX ($I^- > Br^- > Cl^-$) 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 –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 –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 CH_3HgSCH_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 $-SCH_3$ peak areas were measured by 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 (20 000:1) 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.

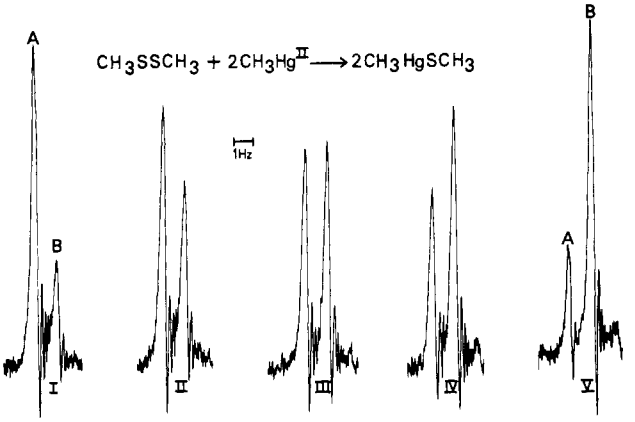

Figure 1. 60-MHz ^1H NMR spectra of the $-SCH_3$ resonances of CH_3SSCH_3 (A) and CH_3HgSCH_3 (B) at intermediate stages of disulfide cleavage.

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 CH_3HgSCH_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 $-SCH_3$ 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 °C (lit.[12] 125.5–127.5 °C). Freshly distilled CH_3SSCH_3 and $P(OEt)_3$ distilled under reduced pressure over sodium metal were added to a 1-mL volumetric flask containing CH_3HgOAc and spectrograde solvent cooled to −15 °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 $(CH_3)_2Hg$ in a concentric capillary tube was used as an external standard. All ^{199}Hg chemical shifts are reported in parts per million relative to $(CH_3)_2Hg$. A negative sign for the chemical shift denotes

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

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(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.

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

expt	CH_3SSCH_3, M	CH_3HgOAc, 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_3SSCH_3, M	CH_3HgOAc, 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 CH_2Cl_2 (1, 3, and 9–13) and $CDCl_3$ (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 CH_3HgOAc was used as the electrophile, the methyl resonance of the reactant CH_3SSCH_3 and product CH_3HgSCH_3 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 CH_3SSCH_3 by the combined action of the electrophile CH_3HgOAc and the nucleophile $P(OEt)_3$.

The rate of –SS– bond scission was followed in the NMR by measuring the loss of CH_3SSCH_3 and the formation of CH_3HgSCH_3 (eq 3). A second mole of CH_3Hg^+ is consumed in a

$$CH_3SSCH_3 + CH_3HgOAc \underset{\text{fast}}{\rightleftharpoons} CH_3\overset{+}{S}SCH_3 + OAc^- \quad (3)$$

(1: $CH_3\overset{+}{S}(HgCH_3)SCH_3$; k_2, slow, $P(OEt)_3$) $\rightarrow CH_3HgSCH_3 + CH_3S\overset{+}{P}(OEt)_3 + OAc^-$

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

$$CH_3S\overset{+}{P}(OEt)_3\bar{O}Ac + CH_3HgOAc \xrightarrow{\text{fast}} CH_3HgSCH_3 + Ac_2O + O{=}P(OEt)_3 \quad (4)$$

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 $-SCH_3$ resonance of the product CH_3HgSCH_3. 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 CH_2Cl_2 to $CDCl_3$. 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.

$$CH_3SSCH_3 + 2CH_3Hg^{II} \longrightarrow 2CH_3HgSCH_3$$

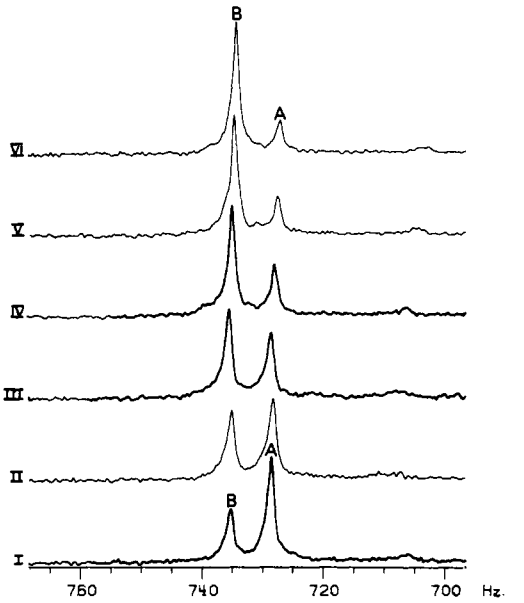


Figure 2. 300-MHz ^1H NMR spectra of the $-SCH_3$ resonances of CH_3SSCH_3 (A) and CH_3HgSCH_3 (B) at intermediate stages of disulfide cleavage.

The pseudo-first-order data, where the rate is $k_1[CH_3SSCH_3]$, was measured while maintaining an excess of both CH_3HgOAc and $P(OEt)_3$. The rate constants were determined by using the rate expression $\ln [(C_1 + C/C_1] = k_1t$, where C_1 is the integrated area for the methyl resonances of CH_3SSCH_3 and C represents the area for the methyl mercaptide protons in CH_3HgSCH_3. 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 CH_3HgOAc to CH_3SSCH_3 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 CH_3SSCH_3 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 $P(OEt)_3$ on the sulfonium ion intermediate **1** (eq 3).

Second-order kinetic behavior was demonstrated at several different concentrations of reactants. The rate of –SS– cleavage is given by $k_{obsd}[CH_3SSCH_3][CH_3HgOAc]$. Actually $k_{obsd} = K_{eq}2k_2[P(OEt)_3]$ 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 $P(OEt)_3$ concentration was reduced to 0.5 M (experiment 15). The rate constants were obtained from the expression $(C/C_1)(1/a) = k_{obsd}t$ 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 $k_{obsd} = 1.24 \times 10^{-2}$ mol^{-1} s^{-1}.

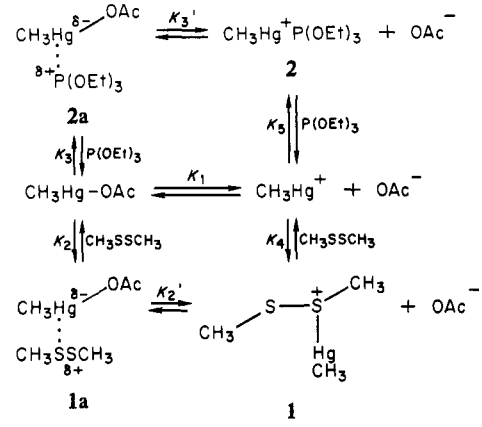
Control experiments have established that neither CH_3HgAOc (24 h) nor $P(OEt)_3$ (48 h) at temperatures as high as 50 °C will effect –SS– bond cleavage. In addition, CH_3SSCH_3 itself is not competing with $P(OEt)_3$ as the effective nucleophile at temperatures up to 80 °C. Triethyl phosphite will, 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 –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 $CH_3HgSC_6H_5$ (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 –SS– bond rupture. We observed no significant change in CH_3SSCH_3 concentration in the presence of 10 equiv of $CH_3HgSC_6H_5$ and 20 equiv of $P(OEt)_3$ after 22 h. This is a particularly significant result since most of the CH_3Hg^{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 CH_3Hg^{II} and $P(OEt)_3$ 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 CH_3Hg^{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 ($K_{stab} \simeq 10^{16}$), there is no data available concerning the positions of equilibria between CH_3Hg^{II} and –SS– or $P(OR)_3$. In the interest of rigor we sought to establish the magnitude of the equilibrium constants that comprise the observed rate constants ($k_{obsd} = K_{eq}k_2[P(OEt)_3]$).

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 CH_3Hg^{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 CH_3Hg^{II} at equilibrium is represented by eq 5,

$$CH_3Hg_{total}^{II} = CH_3Hg_t^{II} + CH_3Hg_t^{II}CH_3SSCH_3 + CH_3Hg_t^{II}P(OEt)_3 \quad (5)$$

where $CH_3Hg_t^{II} = CH_3HgOAc + CH_3Hg^+$, the concentration of CH_3Hg^{II} species with and without an acetate anion in its primary solvent shell.

The three pertinent equilibria involved are therefore

$$K_1 = [ML_1]/([M][L_1]) \qquad K_2 = [M_tL_2]/([M_t][L_2])$$
$$K_3 = [M_tL_3]/([M_t][L_3])$$

where $M = CH_3Hg^+$, $M_t = CH_3Hg_t^{II}$, $L_1 = OAc^-$, $L_2 = CH_3S\text{-}SCH_3$, and $L_3 = P(OEt)_3$. Substitution of these expressions into eq 5 gives eq 6–9, the relative population of the metal species in

$$[M_T] = [ML_1]\left(\frac{1}{K_1[L_1] + 1}\right)(1 + K_1[L_1] + K_3[L_3]) \quad (6)$$

$$[ML_1] = \frac{M_T}{(1 + 1/(K_1[L_1]))(1 + K_2[L_2] + K_3[L_3])} \quad (7)$$

$$[M_TL_2] = [ML_1]\left(1 + \frac{1}{k_1[L_1]}\right)K_2[L_2] \quad (8)$$

$$[M_TL_3] = [ML_1]\left(1 + \frac{1}{K_1[L_1]}\right)(K_3[L_3]) \quad (9)$$

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 $K_2[L_2]/K_3[L_3]$.

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 $J(^{199}Hg\text{–}^1H)$ coupling constant with up to 10 equiv of disulfide at 60 MHz. However, we did see a modest decrease in the $J(^{199}Hg\text{–}^1H)$ coupling constant (212–206 Hz) of CH_3HgOAc in the presence of 10 equiv of $P(OEt)_3$. This is not a significant change since this coupling constant is 156 Hz with a highly covalent mercurial like CH_3HgSCH_3.[2] Similarly, the change in ^{13}C chemical shift was not sufficiently sensitive to the environment of CH_3Hg^{II} to provide a quantitative measure of these equilibrium constants. Even in the presence of 10 equiv of CH_3SSCH_3 or $P(OEt)_3$ 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 –SS–

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Table II. K_f and δ_x Values for $CH_3HgX + L \rightleftarrows CH_3Hg^+XL^-$ (K_f)

expt	X	L	solvent	[MeHgX], mol/L	δ_0	$\delta_x - \delta_0$[a]	K_f eq 13	K_f eq 14	K_f eq 15	K_f eq 16	NMR freq, MHz
16	OAc	CH_3SSCH_3	CH_2Cl_2	0.15	−1080.72	111	0.07	0.06	0.05	0.04[f]	100
							91	101	116	135[g]	
17	OAc	CH_3SSCH_3	CH_2Cl_2	0.15	−1091.50	105	0.06	0.05	0.05	0.05	300
							102	107	106	106	
18	OAc	CH_3SSCH_3	CH_2Cl_2	0.25	−1082.43	89	0.07	0.06	0.06	0.07	100
							83	93	90	89	
19	OAc	CH_3SSCH_3	CH_2Cl_2	0.35	−1083.80	150	0.06	0.06	0.03[f]	0.03[f]	100
							97	99	202	201	
20	OAc	CH_3SSCH_3	MeOH	0.15	−1133.33	60	1.00	1.00	0.89	0.98	300
							59	59	61	60	
21	OC(=O)CF_3	CH_3SSCH_3	CH_2Cl_2	0.15	−1140.13	369	0.09	0.05	0.06	0.06	100
							273	451	374	377	
22	OAc	$P(OEt)_3$	CH_2Cl_2	0.15	−1081.94	244	0.66	0.66	0.59	0.66	100
							243	242	249	240	
23	OAc	$P(OEt)_3$	CH_2Cl_2	0.25	−1082.43	259	0.47	0.47	0.41	0.47	100
							256	256	267	256	
24	OAc	$(n\text{-Bu})_2S$	CH_2Cl_2	0.15	−1090.50	368	0.04	0.03	0.04	0.04	100
							363	456	330	324	
25	Cl[b]	Cl^-	EtOH	0.10	−899.16[b,d]	167	0.28	0.30	0.28	0.29	100
							172	160	170	166	
26	Br[b]	Br^-	EtOH	0.06	−938.51[b,d]	141	1.08	0.99	1.05	1.08	100
							140	146	138	140	
27	OAc	$PhSSCH_3$	CH_2Cl_2	0.15	−1090.52	116	0.06	0.07	0.04[f]	0.05[f]	300
							105	87	147	125	
28	OAc	$(Ph)_2S$[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	CH_3SSCH_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 $[CH_3HgS(CH_3)_2]NO_3$ 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) halides[19] 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

$$\underset{(a-x)}{CH_3HgX} + \underset{(b-x)}{L} \overset{K_f}{\rightleftharpoons} \underset{(x)}{CH_3HgXL}$$

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

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

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

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

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	Δδ, 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-*n*-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 KINFIT4[21] 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 coworkers.[22] In an extensive series of papers they have measured

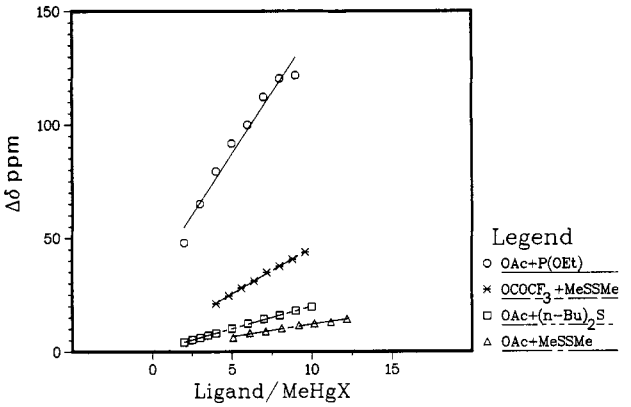

Figure 3. Plot of ^{199}Hg chemical shifts vs. molar ratios of ligand/MeHgX.

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 $((a - x)/a)$

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

instead of (x/a) as in eq 11. We elected to use the molar ratio of complex to free $CH_3Hg^{II}(x/a)$ 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 CH_3HgSCH_3 (experiment 29), the K_f for complexation with a disulfide is too small to measure. The higher donicity of $P(OEt)_3$ 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.

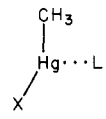
The most striking change in chemical shift was observed upon addition of PhSH to CH_3HgOAc. With a [ligand]/[CH_3HgOAc] ratio of only 1.0, a $\Delta\delta$ of 503.9 ppm was observed which reflects the high K_{stab} ($\sim 10^{16}$) for formation of CH_3HgSPh. When the K_f is high and the concentration 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 polarity[16] when high concentrations of ligand are required to affect a measurable quantity of complex. For example, addition of 10 equiv of the relatively polar (ϵ = 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 $P(OEt)_3$ (ϵ = 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 S_N2 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. [L]/[CH_3HgX] 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]

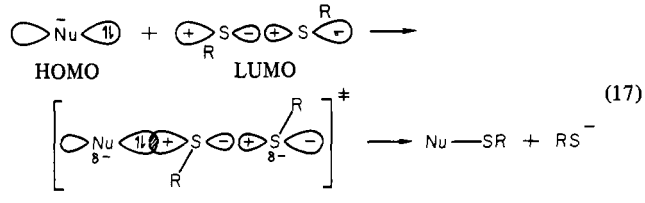
Discussion

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 CH_3Hg^{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 supririsingly low K_f = 0.06 that we have measured. Although most of the CH_3Hg^{II} is present as its $P(OEt)_3$ 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 $P(OEt)_3$. 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 $P(OEt)_3$ (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 –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 –SS– bond rupture and displacement of RS^- (eq 17).



(17)

The displacement of RS^- is, in principle, comparable with a typical S_N2 displacement at saturated carbon, and by analogy, there is no need to invoke a negatively charged intermediate or d orbital participation for the –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 S_N2 pathway for disulfide exchange reactions with thiolate anions.[28b] Similarly Overman has shown that cleavage of the –SS– bond by Ph_3P is rate limiting.[28c] In a particularly interesting report by Kice,[29] it was suggested that nucleophilic displacement at sulfenyl 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]

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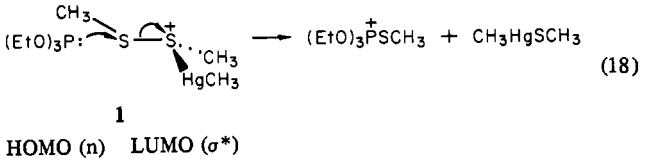
Ab initio calculations[31] have provided convincing evidence that the role of the proton in acid-catalyzed concomitant -SS- scission (eq 2) is to affect an increase in the electron affinity of the disulfide, as evidenced by a marked decrease in the energy of LUMO, and to transform RSE (eq 2) into a neutral leaving group. We attribute the catalytic efficiency of CH_3Hg^{II} to its Lewis acidity which causes a similar lowering of the -SS- σ^* orbital energy upon formation of sulfonium ion **1**. This reduction in energy difference between the frontier molecular orbitals involved in displacement will facilitate the approach of $P(OEt)_3$ and increase the rate of displacement on the low-lying σ^* orbital of **1** (eq 18).



(18)

1

HOMO (n) LUMO (σ^*)

(31) Pappas, J. A. *J. Am. Chem. Soc.* **1977**, *99*, 2926.

In conclusion, we have delineated some of the essential features required for -SS- bond cleavage by CH_3Hg^{II} in a simple disulfide and developed a model system for the study of the interaction of this important functional group with CH_3Hg^{II}. Our kinetic study provides the first mechanistic evidence for a concomitant metal-assisted disulfide cleavage, and we have developed a highly sensitive method for measuring the equilibrium constants for the interaction of the mercury nucleus with a variety of ligands. Most importantly, this study provides a convincing argument that the *disulfide linkage in proteins is not a primary target for methylmercury* since an ionic form of methylmercury is required and essentially all CH_3Hg^{II} in living systems is present as its highly covalent methylmercury mercaptide.

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Xenon–Nitrogen Bonds. The Synthesis and Characterization of [Imidobis(sulfuryl fluoride)]xenon(II) Derivatives $Xe[N(SO_2F)_2]_2$, $FXeN(SO_2F)_2$, and $[(FSO_2)_2NXe]_2F^+AsF_6^-$ and the Radical $\cdot N(SO_2F)_2$

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Abstract: The synthesis and characterization of three compounds containing xenon–nitrogen bonds are described. The novel compounds $Xe[N(SO_2F)_2]_2$ and $FXeN(SO_2F)_2$ are obtained by low-temperature reactions of XeF_2 with the nitrogen acid, $HN(SO_2F)_2$. The complex salt $[(FSO_2)_2NXe]_2F^+AsF_6^-$ is prepared by the reaction of $FXeN(SO_2F)_2$ with AsF_5. The compounds have been characterized by Raman and NMR (^{19}F, ^{129}Xe) spectroscopy. The $\cdot N(SO_2F)_2$ free radical is formed on decomposition of $Xe[N(SO_2F)_2]_2$ and $FXeN(SO_2F)_2$, and its EPR spectrum is reported.

The ability of very electronegative elements to form bonds to xenon in ground-state molecules is now established for fluorine, chlorine, and oxygen.[1] These bonds to xenon may be divided into several types which can be classified informally in the following way: normal xenon–fluorine bonds as found in the binary fluorides such as XeF_2, XeF_4, and XeF_6;[2] bridging xenon–fluorine bonds as found in many complex xenon fluorides like $Xe_2F_3^+AsF_6^-$[3] and $Xe_2F_{11}^+AuF_6^-$;[4] weaker xenon–oxygen bonds as observed in compounds containing xenon bonded to electronegative radicals such as $FXeOC(O)CF_3$[5] and $Xe(OSeF_5)_2$;[6] stronger xenon–oxygen bonds as observed in xenon oxides and oxyfluorides like $OXeF_4$[7] and XeO_3;[8] and weak xenon–chlorine bonds as in $Cs_9(XeO_3Cl_2)_4Cl$.[9] In addition to the above well-established examples, there is good evidence to support the existence of a xenon–xenon bond in Xe_2^+ in solution.[10] Also, preliminary reports have been made on two compounds containing a xenon–nitrogen bond,[11,12] a xenon–boron bond,[13] and a xenon–carbon bond.[14] Thus the total number of elements which form bonds to xenon in compounds isolable under ordinary laboratory conditions is seven or less.

In 1974, the synthesis of $FXeN(SO_2F)_2$ was reported and this provided the first potential example of a xenon–nitrogen bond.[11]

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