bi = 2,2′-bi-2-imidazoline.[6] In this compound, the transition produces a doubling of the high-spin $^5T_2$ lines in the ^{57}Fe Mössbauer spectrum at temperatures lower than the transition temperature $T_c^{ClO_4} \simeq 199$ K. At $T_c^{ClO_4}$, the disorder of the ClO_4 anions is apparently frozen out, each perchlorate assuming one or the other of two possible configurations.

It is therefore suggested that the acetone molecules in $[Fe(dppen)_2Cl_2]\cdot 2(CH_3)_2CO$ are involved in an order–disorder transition centered at $T_c^{acetone} \simeq 240$ K. The transition will result in slight changes of the Fe–P ligation with a consequent effect on the iron sites. In this case, two separate high-spin $^5T_2$ doublets would be expected in the Mössbauer spectrum at $T < T_c^{acetone}$, which should collapse into a single $^5T_2$ doublet above $T_c^{acetone}$. This assumption is fully consistent with the observed broadening of line width discussed above. The conclusion is further supported by the inflection of the effective thickness $t_{s_{T_2}}/t_{total}$ (cf. Figure 3) and the change in slope of the quantity $-\ln(\sum t_i)$ (cf. Figure 4) at that temperature. The maximum in the temperature function of the quadrupole splitting $\Delta E_Q(^5T_2)$ is also found at ~240 K as is the increase of the values for $\Delta E_Q(^1A_1)$ (cf. Figure 2). Since there is no marked change in X-ray diffraction in the region of 240 K, a phase transition at that temperature is ruled out. The suggested order–disorder transition thus should be second or higher order. It is important to note that, in the X-ray structure investigation of the low-spin isomer of $[Fe(dppen)_2Cl_2]\cdot 2(CH_3)_2CO$ at 130 K, ΔF maps show that the acetone molecule is almost equally distributed between two different orientations.[10] The two slightly different iron sites observed in the Mössbauer effect below $T_c^{acetone}$ thus correspond to two different orientations of the acetone molecule. In $[Fe(bi)_3](ClO_4)_2$, the order–disorder transition at $T_c^{ClO_4} \simeq 199$ K and the high-spin ($^5T_2$) $\rightleftharpoons$ low-spin ($^1A_1$) transition at $T_c^{\uparrow} = 114.8$ K (for increasing temperatures) are well separated and are of abrupt character.[6] In the present compound, both the order–disorder transition of the acetone and the spin transition seem to be centered at almost the same temperature and are of a gradual nature. It is therefore very likely that, as the temperature is lowered in the region of the high-spin isomer, the orientationally disordered acetone molecules gradually tend to arrange regularly and thus the order–disorder transition triggers the spin transition that sets in at about 270 K. A similar mechanism has been proposed for the high-spin ($^5T_2$) $\rightleftharpoons$ low-spin ($^1A_1$) transition in $[Fe(2\text{-pic})_3]Cl_2\cdot C_2H_5OH$, where 2-pic = 2-picolylamine.[13] In this compound, the ethanol molecules are hydrogen bonded to the Cl anions and exhibit orientational disorder in the high-spin state, whereas a regular arrangement is observed in the low-spin state. As the spin transition and the order–disorder transition of the ethanol molecule set in, the complex and the ethanol interact through hydrogen bonds. It should be noted that in both $[Fe(dppen)_2X_2]\cdot 2(CH_3)_2CO$, X = Cl, Br, and $[Fe(2\text{-pic})_3]Br_2\cdot C_2H_5OH$ the continuous transition is relatively sharp and almost complete at both temperature ends, whereas if the solvent, acetone or ethanol, is removed from the lattice, the spin transition becomes very gradual and incomplete at low as well as high temperatures.[9,10,23] This suggests that, in the present compound, intermolecular interactions between the complex and the solvent molecule are important and possibly assist in the propagation of the spin transition through the lattice.

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Nuclear Magnetic Resonance Studies of the Solution Chemistry of Metal Complexes. 20. Ligand-Exchange Kinetics of Methylmercury(II)–Thiol Complexes

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The kinetics of the exchange of methylmercury, CH_3Hg^{II}, between thiol ligands in aqueous solution was studied by ^1H NMR spectroscopy over a range of pH values. Exchange of CH_3Hg^{II} between two different mercaptoacetic acid ligands and between mercaptoacetic acid and cysteine, penicillamine, or glutathione was found to be by displacement of complexed thiol by free thiol at pH >1. The exchange rate is pH dependent due to the effect of protonation of the ligand. For the amino acid and peptide ligands, exchange at physiological pH is predominantly via displacement of complexed mercaptoacetic acid by the amino-protonated, thiol-deprotonated form of the displacing ligand. At pH <1, exchange is predominantly via proton-assisted dissociation of the complex followed by reaction of CH_3Hg^{II} with free thiol. The second-order rate constants for displacement of complexed thiol by free thiol are consistent with an associative mechanism, in which the exchange rate constant is determined by the free energy difference between the two complexes.

Introduction

The mechanism by which the methylmercury cation, CH_3Hg^{II}, is exchanged between thiol ligands is of both chemical and biological interest. CH_3Hg^{II}–thiol complexes are very stable thermodynamically, having formation constants in the 10^{15}–10^{17} range.[1-4] However, they are very labile, as indicated by the observation of exchange-averaged resonances in ^1H and ^{13}C NMR spectra for thiol ligands in solutions containing CH_3Hg^{II} and an excess of thiol.[3-7] CH_3Hg^{II} is also apparently quite labile in biological systems, exchanging among the multitude of thiol ligands it encounters, with some ultimately combining with thiol ligands in the central nervous system.[8] Consistent with this, exchange-averaged ^1H reso-

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nances are observed for the thiol-containing tripeptide glutathione (GSH) in intact human erythrocytes that contain CH_3Hg^{II}.[9] The average lifetime of the CH_3Hg^{II}–GSH complex is estimated to be less than 0.01 s, which indicates exchange of CH_3Hg^{II} between thiol ligands to be fast in the cell.

In this paper, we report the results of an ^1H NMR study of the kinetics of exchange of CH_3Hg^{II} between thiol ligands in aqueous solution. The exchange reactions studied include the exchange of CH_3Hg^{II} between two different mercaptoacetic acid (MAA) ligands, and between MAA and penicillamine (PSH), cysteine (CSH), or GSH. Exchange pathways were elucidated from the dependence of exchange rates on solution pH. The results are consistent with an associative mechanism, which predicts the ligand exchange rate constant to be related to the free energy difference between the two complexes.[10]

Experimental Section

Mercaptoacetic acid (Eastman Kodak Co.), cysteine and penicillamine (Aldrich Chemical Co.), and glutathione (Sigma Chemical Co.) were used as received. The determination of purity and the preparation of solutions were by procedures described previously.[3]

Methylmercury(II) iodide (Alfa Division, Ventron Corp.) was converted to a solution of methylmercury(II) hydroxide and standardized by titration with chloride as described previously.[3] All solutions were prepared with water that was doubly distilled and then deionized by passage through a Barnstead D8902 Ultrapure mixed-bed ion-exchange resin.

pH measurements were made as described previously.[3] ^1H NMR spectra were obtained at 25 ± 1 °C on a Varian A60D spectrometer. Spectra were recorded at a sweep rate of 0.1 Hz s^{-1}. Chemical shifts were measured relative to either the central resonance of the triplet for the tetramethylammonium ion or the singlet for 1,4-dioxane. A small amount of reference compound was added to solutions before pH adjustments. Spectrometer frequency sweep widths were calibrated by resonance modulation with a low-audio-frequency signal (Hewlett-Packard Model 200 AB audio signal generator). The peak-to-valley ratio of the three components of the triplet resonance for the tetramethylammonium ion (splitting of 0.5 Hz) was used as a criterion of spectrometer resolution when resonance line widths were measured for lifetime determinations.

Solutions were prepared by mixing stock solutions of CH_3Hg^{II} and MAA to give a 1:1 ratio and then adding a known amount of another thiol (PSH, CSH, GSH, or MAA itself). Samples were withdrawn for NMR measurements at selected pH values as the pH was adjusted by addition of HNO_3 or NaOH. Both the chemical shift and the line width of the MAA resonance were determined. For all solution conditions, a single averaged resonance was observed for MAA, indicating exchange of MAA between the free and complexed forms. As discussed below, the width of the resonance and thus the rate of exchange is a function of pH and solution composition. The fraction of MAA in the free and complexed forms was calculated from the exchange-averaged chemical shift by procedures described previously.[3]

The lifetime of MAA in the complexed form, τ_c, was obtained from the line width of the exchange-averaged MAA resonance by simulation of spectra with Bloch equations modified to account for interchange of nuclei between two chemical environments.[11] Spectra were simulated as a function of τ_c until the width at half-height of the simulated spectrum matched that of the experimental spectrum.

Results

MAA–MAA Exchange Kinetics. MAA reacts with CH_3Hg^{II} to form the complex $CH_3HgSCH_2CO_2H$, which has a carboxylic acid group pK_A of 3.80.[3] An exchange-averaged resonance is observed for the methylene protons of MAA in ^1H NMR spectra of solutions containing MAA in excess over CH_3Hg^{II}. The width at half-height ($W_{1/2}$) of the resonance is dependent on pH and concentration; typical results are shown in Figure 1. It is obvious from these data that the rate

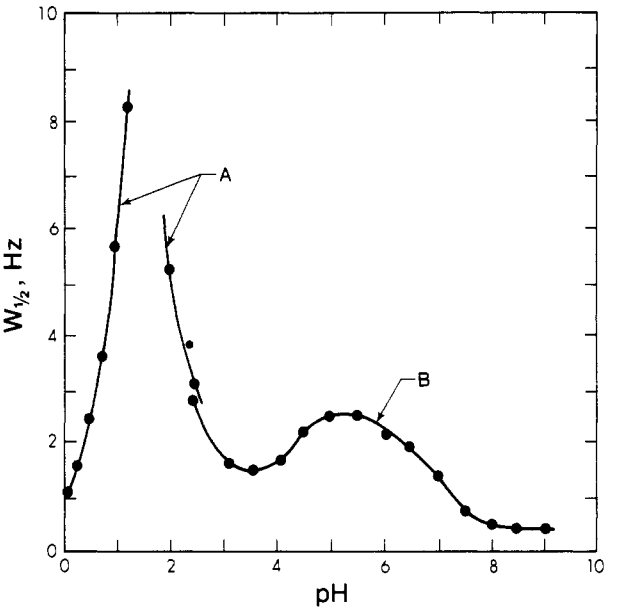

Figure 1. Width at half-height of the MAA methylene resonance as a function of pH for solutions containing (A) 0.17 M MAA and 0.09 M CH_3Hg^{II} and (B) 0.21 M MAA and 0.13 M CH_3Hg^{II}. The curves are drawn to connect the data points from the two separate experiments.

of exchange is different in different pH regions, indicating that there are several pH-dependent pathways for exchange of MAA between the free and complexed forms.

The lifetime of MAA in the complexed form, τ_c, was obtained from the $W_{1/2}$ of exchange-broadened resonances as described above. The inverse of τ_c is related to the rate of decrease in the concentration of the complex by

$$\frac{1}{\tau_c} = \frac{-d[C]}{dt}\frac{1}{[C]} \quad (1)$$

The simplest rate equation that fits the lifetime data over the pH range 0–8 is

$$-d[C]/dt = [CH_3HgSCH_2CO_2^-][^-SCH_2CO_2^-](k_1 + k_2a_H + k_3a_H^2 + k_4a_H^3) + k_H[CH_3HgSCH_2CO_2H]a_H \quad (2)$$

where a_H is the activity of the hydrogen ion. Rate constant k_1 is for the displacement of complexed MAA by fully deprotonated free MAA; rate constants k_2–k_4 are also for displacement of complexed MAA by free MAA but with one or both reactants in various stages of protonation. The last term is for exchange by a pathway involving proton-assisted dissociation of the complex. The rate equation is discussed in more detail in the Discussion.

Substitution of $\alpha_b[C]$, $\alpha_p[C]$, and $\alpha_f[MAA]_f$, where $\alpha_b = K_A/(K_A + a_H)$, $\alpha_p = 1 - \alpha_b$, $[C] = [CH_3HgSCH_2CO_2^-] + [CH_3HgSCH_2CO_2H]$, and $\alpha_f = K_{A1}K_{A2}/(a_H^2 + a_HK_{A1} + K_{A1}K_{A2})$, for $[CH_3HgSCH_2CO_2^-]$, $[CH_3HgSCH_2CO_2H]$, and $[^-SCH_2CO_2^-]$ in eq 2, respectively, and division by [C] yields

$$1/\tau_c = \alpha_b\alpha_f[MAA]_f(k_1 + k_2a_H + k_3a_H^2 + k_4a_H^3) + \alpha_pk_Ha_H \quad (3)$$

K_A is the acid dissociation constant for $CH_3HGSCH_2CO_2H$, and K_{A1} and K_{A2} are the acid dissociation constants for $HSCH_2CO_2H$. The five rate constants were evaluated by treating data in the different regions with the appropriate reduced forms of eq 3.

Data between pH 9 and 5.5 were fitted to the equation

$$1/\tau_c = \alpha_b\alpha_f[MAA]_f(k_1 + k_2a_H) \quad (4)$$

Values obtained for k_1 and k_2 from the intercept and slope

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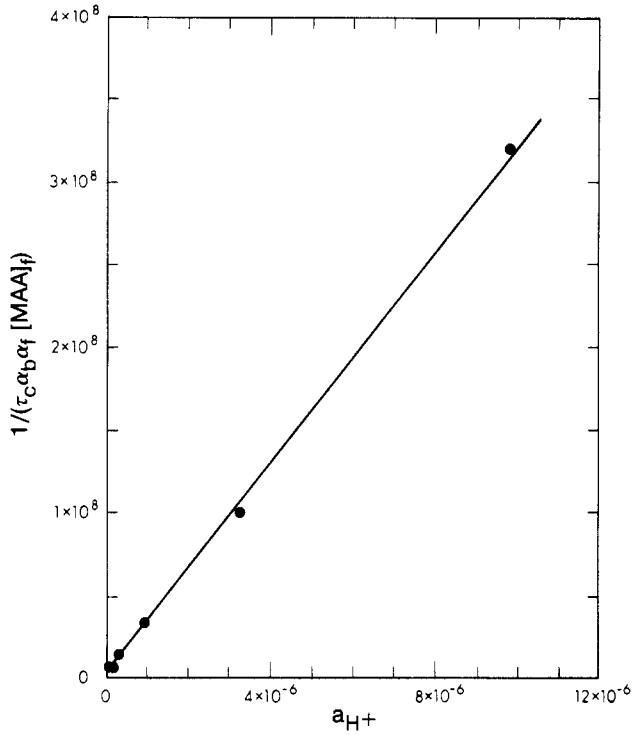

Figure 2. Plot of $1/(\tau_c\alpha_b\alpha_f[MAA]_f)$ vs. a_H to evaluate k_1 and k_2 for MAA self-exchange.

Table I. Rate Constants for the Exchange of Mercaptoacetic Acid between Free and Complexed Forms

rate const	value of rate const	rate const	value of rate const
k_1	5.8×10^6 L/(mol s)	k_4	1.4×10^{20} L^4/(mol^4 s)
k_2	3.2×10^{13} L^2/(mol^2 s)	k_H	900 L/(mol s)
k_3	0.9×10^{18} L^3/(mol^3 s)		

of the linear least-squares fit[12] of $1/(\tau_c\alpha_b\alpha_f[MAA]_f)$ vs. a_H in Figure 2 are listed in Table I.

Data between pH 5 and 2.5 were fitted to the equation

$$1/\tau_c = \alpha_b\alpha_f[MAA]_f(k_2a_H + k_3a_H^2 + k_4a_H^3) \quad (5)$$

The values obtained for k_3 and k_4 from the linear least-squares intercept and slope of a plot of $(1/\tau_c - \alpha_b\alpha_f[MAA]_fk_2a_H)/(\alpha_b\alpha_f[MAA]_fa_H^2)$ vs. a_H are given in Table I.

Data in the pH region 0–1 were fitted to the equation

$$1/\tau_c = \alpha_b\alpha_f[MAA]_f(k_3a_H^2 + k_4a_H^3) + k_H\alpha_pa_H \quad (6)$$

A value of 900 L/(mol s) was obtained for k_H from the linear least-squares slope of the plot of $(1/\tau_c - \alpha_b\alpha_f[MAA]_f(k_3a_H^2 + k_4a_H^3))/\alpha_p$ vs. a_H in Figure 3. For comparison, the rate constant for the proton-assisted dissociation of the CH_3Hg^{II}–GSH complex is 600 L/(mol s).[5]

Exchange of CH_3Hg^{II} between MAA and Other Thiols. The chemical shift of the resonance for the methylene protons of MAA in a solution containing CH_3Hg^{II}, MAA, and PSH, CSH, or GSH at a 1:1:1 ratio is intermediate between those of free and complexed MAA, indicating that some of the CH_3Hg^{II} is complexed by the other thiol. From the exchange-averaged chemical shift, the fractions of MAA in the free and complexed forms can be calculated.[3] The $W_{1/2}$ of the exchange-averaged MAA resonance is less than that calculated from the τ_c predicted by the rate constants determined in the previous section and the concentrations of free and complexed MAA. This indicates that additional pathways exist by which MAA can exchange between its free and complexed forms when the solution contains another thiol.

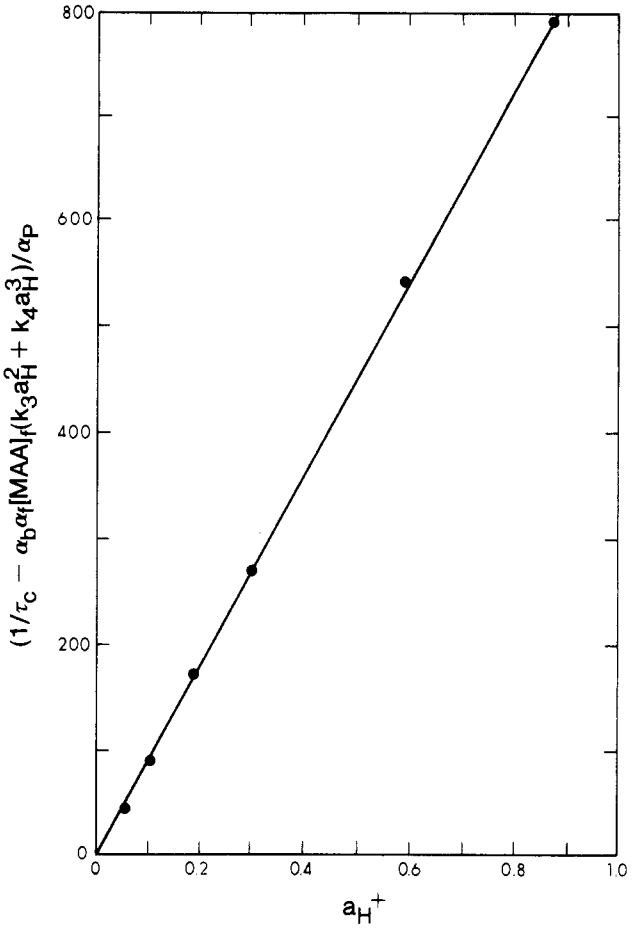

Figure 3. Plot of $1/\tau_c - (\alpha_b\alpha_f[MAA]_f(K_3a_H^2 + k_4a_H^3))/\alpha_p$ vs. a_H to evaluate k_H from MAA self-exchange.

Table II. Rate Constants for the Displacement of Complexed Mercaptoacetic Acid by Other Thiols

thiol	k_5, L^2/(mol^2 s)	k_6, L^3/(mol^3 s)
penicillamine[a]	3.1×10^{16}	8.4×10^{21}
cysteine[b]	5.7×10^{16}	1.8×10^{22}
glutathione[c]	2.0×10^{16}	1.3×10^{22}

[a] Derived from data covering the pH range 4.5–7.5. [b] Derived from data covering the pH range 4.5–7. [c] Derived from data covering the pH range 4–6.5.

Exchange kinetics data from the pH region 4.5–7.5 for solutions containing CH_3Hg^{II}, MAA, and PSH were analyzed as described above. The rate equation, in terms of the lifetime of the CH_3Hg^{II}–MAA complex, that fits the data is

$$1/\tau_c = \alpha_b\alpha_f[MAA]_f(k_1 + k_2a_H + k_3a_H^2) + \alpha[PSH]_f(k_5a_H + k_6a_H^2) \quad (7)$$

where α is the fraction of free PSH which is fully deprotonated; $\alpha = K_{A2}K_{A3}/(a_H^2 + a_HK_{A2} + K_{A2}K_{A3})$, and K_{A2} and K_{A3} are the second and third acid dissociation constants for PSH. The first term on the right-hand side of eq 7 accounts for the displacement of complexed MAA by free MAA; the second term is for displacement of complexed MAA by free PSH. The $k_4a_H^3$ term in eq 3 is omitted since it is negligible relative to $k_1 + k_2a_H + k_3a_H^2$ in this pH region. Rate constants k_5 and k_6 were obtained as the linear least-squares intercept and slope of a plot of $(1/\tau_c - \alpha_b\alpha_f[MAA]_f(k_1 + k_2a_H + k_3a_H^2))/(\alpha[PSH]_fa_H)$ vs. a_H. The results are listed in Table II.

Exchange kinetic data for solutions containing CH_3Hg^{II}, MAA, and CSH or GSH were analyzed by the same proce-

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dure. Values obtained for k_5 and k_6 for CSH, from data over the pH range 4.5–7, are listed in Table II. Values obtained for GSH from data for the pH range 4–6.5 are also listed in Table II.

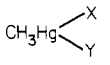
At pH less than 1, exchange is almost completely by proton-assisted dissociation of the $CH_3HgSCH_2CO_2H$ complex, the k_H term in eq 2. Since this term involves no free thiol species, the apparent rate of MAA exchange in the pH region 0–1 is predicted to be independent of the concentration and identity of free thiols present. Estimates of 900, 1200, and 600 (±300) L/(mol s) were obtained for k_H from pH 0–1 data for solutions containing CH_3Hg^{II}, MAA, and PSH, CSH, or GSH, respectively, in reasonable agreement with the value obtained from the MAA self-exchange data.

Discussion

CH_3Hg^{II} Ligand-Exchange Reactions. Three distinct reaction pathways by which CH_3Hg^{II} can exchange among ligands have been identified. The most common pathway involves displacement of complexed ligand by free ligand:[10,13]

$$CH_3HgX + Y \underset{k_-}{\overset{k}{\rightleftharpoons}} CH_3HgY + X \qquad (8)$$

Geier and co-workers have shown this to be an important pathway for X = OH^-, pyridine ligands, or thiones and Y = a variety of ligand types.[10,14-16] The reaction proceeds via an associative mechanism, involving the intermediate

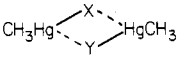


in which Hg has expanded its coordination number. The tendency of the intermediate to dissociate to reactants or products and, thus, the rate of exchange depend on the relative stabilities of the two complexes. When K_f of CH_3HgX is larger than that of CH_3HgY, $k < k_-$, and k_- increases with increases in K_f of CH_3HgY. The maximum value of k is limited by the rate at which the reactants can diffuse together.

A second reaction pathway involves "direct exchange"

$$CH_3HgX + CH_3Hg^*Y \rightleftharpoons CH_3HgY + CH_3Hg^*X \qquad (9)$$

through the four-centered bridged intermediate[6,13,17]



Bach and Weibel have demonstrated this to be a probable pathway in CH_3Hg^{II}–thiol exchange.[6] It is unlikely that this pathway is important in the toxicology of CH_3Hg^{II} since it does not result in the transfer to free ligands.

A third possible exchange pathway is via dissociation of the complex followed by reaction of the aquated CH_3Hg^{II} with another ligand.[10] Although this mechanism has been claimed to be operative in *N*-acetylcysteine–chloride exchange at CH_3Hg^{II},[18] it is too slow to be important for CH_3Hg^{II}–thiol exchange on the NMR time scale.[5] Since the formation constants of CH_3Hg^{II}–thiol complexes are on the order of 10^{16} L/mol and the formation rate constants can be no larger than a diffusion-controlled bimolecular rate constant ($\sim 10^{10}$ L/(mol s)), the dissociation rate constant can be no greater than 10^{-6} s^{-1}. At low pH, however, the proton-assisted dissociation process

$$CH_3HgSR + H^+ \rightleftharpoons CH_3Hg^{II} + RSH \qquad (10)$$

provides an important pathway for CH_3Hg^{II}–thiol exchange.[5] The reaction proceeds via protonation of the CH_3Hg^{II}-complexed sulfur, which results in a complex that has a much lower formation constant. Thus, at low pH, direct dissociation of the protonated complex can contribute appreciably to the lability of the system.

MAA–MAA Exchange Reactions. The kinetics of exchange of MAA between its complexed and free forms are described by eq 2. Rate constants k_1–k_4 are for displacement of complexed ligand by free ligand; rate constant k_H is for exchange by proton-assisted dissociation of the complex. There are no terms in the rate equation for direct exchange of the type represented by eq 9 since such a reaction would not contribute to exchange of MAA between its free and complexed forms.

Rate constant k_1 is for the displacement of complexed MAA by fully deprotonated MAA. Since the associative intermediate that forms has two identical ligands bonded to the CH_3Hg^{II}, there is equal probability of dissociation to reactants or products. If formation of the intermediate is diffusion controlled, the value listed in Table I for k_1 is small by the standards of typical bimolecular diffusion-controlled rate constants (log $k \approx 9.5$),[10] probably because of strong charge repulsion between the singly charged complex and the doubly charged free ligand.

Apparent rate constants k_2–k_4 are also for pathways involving displacement of complexed ligand by free ligand, but in addition they involve 1, 2, or 3 hydrogen ions, respectively. Third or higher order reactions are not implied; rather, the protons are ligand bound. There are three possible protonation sites, the carboxylate groups of free and bound MAA and the thiolate group of free MAA, and thus three different exchange reactions can be written for process 2. It is not possible to assign process 2 to one of these reactions since they are kinetically indistinguishable. The thiolate group is the most basic site; however, the species $HSCH_2CO_2^-$ is probably not very effective at displacing complexed MAA. The rate constant derived from the value for k_2 in Table I and the pK_A[3] of $HSCH_2CO_2^-$ is 2.7×10^3 L/(mol s). The species $CH_3HgSCH_2CO_2H$ and $^-SCH_2CO_2H$ will be of low abundance relative to $HSCH_2CO_2^-$; however, they still could be kinetically important if the rate constants were large enough. The rate constant derived from the value for k_2 in Table I and the pK_A[3] of $CH_3HgSCH_2CO_2H$ for the pathway involving displacement of $CH_3HgSCH_2CO_2H$ by $^-SCH_2CO_2^-$ is 5.1×10^9 L/(mol s), which is close to the diffusion-controlled limit. A value cannot be derived for the alternative reaction of $CH_3HgSCH_2CO_2^-$ with $^-SCH_2CO_2H$ since the pK_A of the carboxylate group in this free ligand species is not known.

Three different exchange reactions involving different protonated species can be written for the pathway accounted for by k_3; however, as with k_2 it is not possible to distinguish between them from the kinetic data. In the pathway accounted for by k_4, the three protons are presumably on the two carboxylate groups and the thiolate group. The rate constant derived from the value for k_4 in Table I and the pK_A's of the protonated groups[3] for the reaction of $HSCH_2CO_2H$ with $CH_3HgSCH_2CO_2H$ is 5.8×10^2 L/(mol s). Since this reaction involves neutral species, its rate constant is expected to be larger than that calculated above for the reaction of $CH_3HgSCH_2CO_2^-$ with $HSCH_2CO_2^-$, suggesting that the reaction accounted for by k_2 involves a carboxlate-protonated species rather than $CH_3HgSCH_2CO_2^-$ and $HSCH_2CO_2^-$.

This appears to be the first time that the exchange kinetics of a thiol ligand at CH_3Hg^{II} have been characterized in such detail. The observation of anomalously slow kinetics for the displacement of complexed MAA by $^-SCH_2CO_2^-$ is especially significant. Similar behavior would be anticipated for mer-

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Table III. Reacting Species and Rate Constants for the Exchange of Mercaptoacetic Acid between Free and Complexed Forms

$$CH_3HgA + B \rightleftarrows CH_3HgB + A$$

no.[a]	A[b]	B	k, L/(mol s)	log (K_{fB}/K_{fA})[c]
1	$^-SCH_2CO_2^-$	$^-SCH_2CO_2^-$	5.8×10^6	0
2	$^-SCH_2CO_2^-$	PS^- (S^-, NH_3^+)[d]	1.6×10^6	−2.13
3	$^-SCH_2CO_2^-$	CS^- (S^-, NH_3^+)	4.6×10^6	−1.54
4	$^-SCH_2CO_2^-$	GS^{2-} (S^-, NH_3^+)	1.66×10^7	−1.07
5	PS^- (NH_3^+)	$^-SCH_2CO_2^-$	1.18×10^8	2.13
6	CS^- (NH_3^+)	$^-SCH_2CO_2^-$	1.61×10^8	1.54
7	GS^{2-} (NH_3^+)	$^-SCH_2CO_2^-$	1.95×10^8	1.07

[a] Numbers refer to data points in Figure 4. [b] Thiolate coordinated. [c] Formation constants of the CH_3Hg^{II} complexes of A and B; from ref 3. [d] PS^- indicates penicillamine with an overall charge of 1−; (S^-, NH_3^+) indicates the thiol group is deprotonated and the amino group protonated.

capto- and 2,3-dimercaptosuccinic acids, which are two of the most successful antidotes for treating CH_3Hg^{II} poisoning. Consistent with this prediction, it has been observed that, in hemolyzed erythrocytes, CH_3Hg^{II} complexes of these ligands are kinetically more stable than complexes with other thiols.[19]

Displacement of Complexed MAA by Other Thiols. The reactions by which PSH, CSH, and GSH displace complexed MAA involve one or two protons. The most basic sites of the reacting species are the thiolate and amino groups. The amino group is most likely protonated in the process accounted for by k_5 since, as discussed above, protonation of the thiol group is expected to decrease its effectiveness at displacing MAA. The rate constants derived from the values listed in Table II for k_5 and the microscopic pK_A's for the ammonium groups[3,4] for the displacement of complexed MAA by the thiol-deprotonated, amino-protonated forms of PSH, CSH, and GSH are listed in Table III. Since the equilibrium constant for the reaction represented by eq 8 is a ratio of displacement rate constants, rate constants can be calculated for the reverse reaction from the forward rate constant and K_{eq}, which can be calculated from the formation constants reported previously for these complexes.[3,4] The rate constants obtained in this way for the displacement of the thiol-complexed, amino-protonated forms of PSH, CSH, and GSH from their CH_3Hg^{II} complexes by $^-SCH_2CO_2^-$ are also listed in Table III.

The second proton in the exchange reaction accounted for by k_6 could be on the thiol group of the displacing ligand or on a carboxylate group of either the complexed MAA or the displacing ligand. As discussed above, protonation of the thiol group is expected to decrease its reactivity considerably. Of the carboxylate groups, that of $CH_3HgSCH_2CO_2^-$ is considerably more basic, suggesting it to be the site of protonation by the second proton. The rate constants derived from the values for k_6 in Table II for the process in which one proton is on the amino group of the reacting ligand are 1.7×10^{12}, 3.3×10^{12}, and 1.1×10^{13} $L^2/(mol^2\ s)$ for PSH, CSH, and GSH, respectively. These values are similar to that for k_2 in Table I, which is for the analogous process involving MAA.

Reaction Mechanism. Rate constants for CH_3Hg^{II} exchange reactions in which free ligand displaces complexed ligand (eq 8) depend on the relative formation constants of the two complexes if they proceed via an associative mechanism.[10] The solid curve in Figure 4 shows the dependence of rate constant on the relative formation constants according to the theory of Geier and co-workers.[10] Also plotted in Figure 4 are exchange rate constants from Table III. The shape of the curve results from theory; however, its vertical position depends on the value for the diffusion-controlled limit for a bimolecular reaction. The theoretical curve was calculated for a limiting value of 2×10^8 L/(mol s). This value is somewhat less than the maximum value possible for diffusion-controlled rate constants;[10] however, the reactions in Table III all involve highly charged intermediates formed by diffusion together of like-charged species. Also, the reactants are relatively large and probably nonspherical, and thus their diffusion rates are likely to be less than maximum.

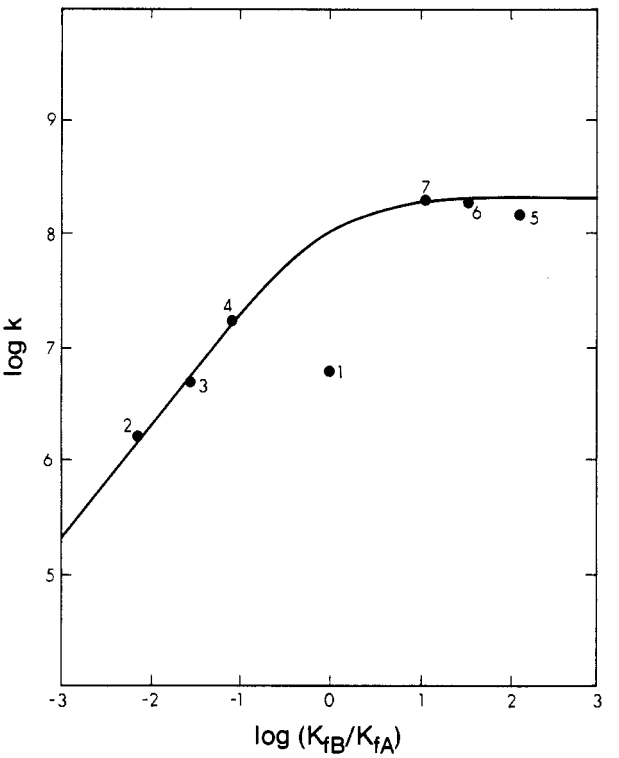

Figure 4. Dependence of rate constants for thiol ligand exchange on relative formation constants of the complexes. The numbers refer to data points in Table III. The solid curve through the points is the log k − log (K_{fB}/K_{fA}) dependence predicted by the theory of Geier and co-workers[10] for exchange via an associative mechanism with a limiting bimolecular rate constant of 2×10^8 L/(mol s).

The data in Figure 4 clearly follow the expected trend for an associative mechanism. The only point that is significantly off the curve is that for MAA/MAA exchange, the rate of which, as discussed above, is probably slower than expected due to the proximity of the negative charges on the carboxylate groups in both the displacing and leaving ligands.

Summary

The results of this study indicate that, in solutions containing an excess of thiol, CH_3Hg^{II} exchanges rapidly among thiol ligands by displacement of complexed ligand by free ligand via an associative mechanism. Since the symptoms of methylmercury poisoning begin at CH_3Hg^{II} levels far below cellular thiol levels, these are the conditions present in methylmercury poisoning.[8] These also are the conditions under which CH_3Hg^{II} has been observed by ^1H NMR to exchange rapidly between GSH molecules in the intracellular region of intact erythrocytes.[9] It seems reasonable to propose that displacement of complexed thiol by free thiol is the major pathway by which CH_3Hg^{II} exchanges among thiol ligands in biological systems.

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Registry No. MAA, 68-11-1; PSH, 52-67-5; CSH, 52-90-4; GSH, 70-18-8; $CH_3HgSCH_2CO_2H$, 61099-81-8.

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