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Nuclear Magnetic Resonance Studies of the Solution Chemistry of Metal Complexes. 16. Complexation of Trimethyllead by Sulfhydryl-Containing Amino Acids and Related Molecules

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The complexation of trimethyllead (TML), $(CH_3)_3Pb^{IV}$, by the amino acids cysteine, penicillamine, and glycine and by *N*-acetylpenicillamine and mercaptoethanol has been studied by ^1H nuclear magnetic resonance spectroscopy. Of the potential binding sites in these ligands, the deprotonated sulfhydryl group binds $(CH_3)_3Pb^{IV}$ most strongly at intermediate and high pH. The amount of binding is pH dependent due to competitive protonation of the sulfhydryl group at low pH and competitive complexation of $(CH_3)_3Pb^{IV}$ by hydroxide ion at high pH. At low pH, there is also some complexation by the carboxylate groups. It is shown that $(CH_3)_3Pb^{IV}$ can bind to the sulfhydryl group with one-to-one and, in some cases, two-to-one $(CH_3)_3Pb^{IV}$-to-sulfhydryl stoichiometry; no evidence was obtained for binding with one-to-two stoichiometry. Exchange of TML among its various complexed forms is rapid on the NMR time scale. From exchange-averaged chemical shifts, formation constants have been calculated for complexation of $(CH_3)_3Pb^{IV}$ by carboxylate and by sulfhydryl groups, including microscopic formation constants for sulfhydryl complexes in which the amino groups are protonated.

Introduction

There is presently considerable interest in the aqueous coordination chemistry of organometallic forms of heavy metals, e.g., alkyl forms of mercury and lead, since their aqueous coordination chemistry most likely determines to some extent their behavior in biological systems. Studies of the aqueous coordination chemistry of methylmercury, CH_3Hg^{II}, have shown for example, that, of the potential binding sites in amino acids, peptides, and proteins, sulfhydryl groups have the highest affinity for CH_3Hg^{II} and have provided insight into the behavior, for example, the mobility, of CH_3Hg^{II} in biological systems.[1,2]

Of the various organometallic forms of lead, the trialkyllead(IV) species are of particular interest. Inhalation or absorption of tetraalkyllead compounds results in lead in the fluids and tissues of the body, primarily as trialkyllead(IV) salts,[3,4] and certain microorganisms are now thought to be able to methylate lead.[5-7] To date, chelation therapy, a common form of treatment for inorganic lead poisoning, has proven to be ineffective as a treatment for organolead poisoning because of the lack of chelating agents for organo forms of lead.[3,4] Indeed, there have been few reports describing the aqueous coordination chemistry of the organo compounds of lead.

Because the sulfhydryl group is known to have a strong affinity for inorganic lead,[8,9] we have studied the aqueous coordination chemistry of trimethyllead (TML, $(CH_3)_3Pb^{IV}$) with several sulfhydryl-containing amino acids and related ligands. The ligands studied include mercaptoethanol, cysteine, penicillamine, and *N*-acetylpenicillamine. The latter two ligands were included because of their effectiveness in the treatment of other forms of heavy-metal poisoning.[10,11] The complexation reactions have been studied by ^1H NMR by monitoring the exchange-averaged resonances for the $(CH_3)_3Pb^{IV}$ protons. Formation constants for the binding of $(CH_3)_3Pb^{IV}$ by the sulfhydryl groups of these ligands, including microscopic formation constants for complexes with amino protonated forms of cysteine and penicillamine, have been derived from the chemical shift data.

Experimental Section

Chemicals. Trimethyllead acetate (Alfa Inorganics) was used as the source of trimethyllead. Because acetate forms a complex with $(CH_3)_3Pb^+$ in aqueous solution, it was converted to a stock solution of trimethyllead perchlorate by an ion-exchange procedure described previously.[12] The stock solution was standardized by potentiometric titration.

The ligands were used as received. They were stored at 4 °C, and the purity with respect to sulfhydryl content was determined for each ligand. The purity of 2-mercaptoethanol was determined by titration with base to be 97.2 ± 0.6% $HOCH_2CH_2SH$; by ^1H NMR the mercaptoethanol was determined to be 97% in the sulfhydryl form, 1.5% disulfide, and 1.5% water. Neither impurity interferes with the formation constant study. *N*-Acetyl-D,L-penicillamine was found to be 99.1 ± 0.4% pure by an acid–base titration procedure and 98.7 ± 1.0% by reaction of the sulfhydryl groups with iodacetamide and titration of the protons released with base.[13] The purities of the L-cysteine and D,L-penicillamine were determined to be 95.0 ± 0.5% and 99.6 ± 0.4%, respectively, by titration with coulometrically generated bromine in 1 M HCl, by using biamperometric end-point detection.[14]

Sample Preparation. All solutions were prepared with doubly distilled water which had been freshly boiled and cooled under a stream of argon. Most NMR measurements involved measuring of the trimethyllead chemical shift as a function of pH for a solution containing trimethyllead and ligand at a constant ratio. The solutions were prepared from stock trimethyllead perchlorate solution, and ligand was added either as a solid or as an aliquot of a standardized solution. The ionic strength was adjusted to 0.3 M with $NaClO_4$, and *tert*-butyl alcohol was added as a chemical shift reference. The solutions were usually made acidic (pH ~2.5) with perchloric acid, and then sodium hydroxide was added and NMR samples were withdrawn at pH intervals of ~0.4 pH unit up to pH ~12.5. For minimization of air oxidation of ligand sulfhydryl groups, sample preparation was done under a stream of argon, and NMR spectra were run immediately after preparation. The trimethyllead concentration in the solutions used in the NMR measurements was either 0.005 or 0.010 M, and the ratio of ligand to trimethyllead varied between 0.5 and 10 but

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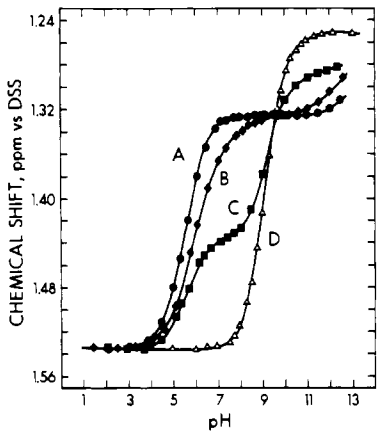

Figure 1. pH dependence of the chemical shift of TML in solutions of (A) 0.0100 M TML and 0.0200 M 2-mercaptoethanol, (B) 0.0100 M TML and 0.00970 M 2-mercaptoethanol, (C) 0.0200 M TML and 0.0100 M 2-mercaptoethanol, and (D) 0.0100 M TML (0.3 M ionic strength and 25 °C).

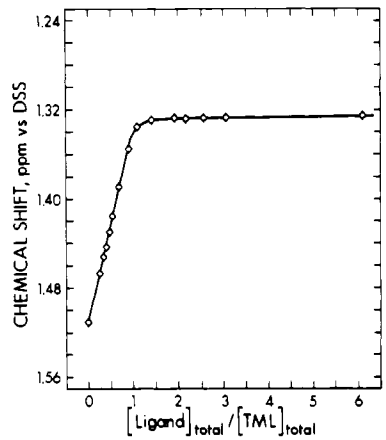

Figure 2. Chemical shift of TML as a function of the 2-mercaptoethanol to TML ratio at pH 8.0. The 2-mercaptoethanol concentration was constant at 0.00887 M except at the ratio of zero (0.3 M ionic strength and 25 °C).

generally was either 2 or 4. In the mole ratio experiment with trimethyllead and mercaptoethanol, each sample solution was made separately with a particular trimethyllead to mercaptoethanol ratio but a constant ionic strength and pH.

pH measurements were made at 25 ± 1 °C with an Orion 701 pH meter equipped with a standard full-range glass electrode and an Ag/AgCl reference electrode in which saturated Na_2SO_4 was used as the electrolyte solution. This solution was used in the reference electrode rather than the standard KCl electrolyte to avoid problems resulting from the precipitation of $KClO_4$ in the reference-electrode fiber junction.

NMR Measurements. ^1H NMR spectra were obtained on a Varian A-60-D spectrometer at a probe temperature of 25 ± 1 °C. Chemical shifts were measured relative to the *tert*-butyl resonance of *tert*-butyl alcohol but are reported relative to the methyl resonance of sodium 2,2-dimethyl-2-silapentane-5-sulfonic acid (DSS). The *tert*-butyl alcohol resonance is 1.243 ppm downfield from the methyl resonance of DSS.

Calculation of Formation Constants. Formation constants for the complexation of TML by the sulfhydryl-containing ligands were calculated from the chemical shift of the methyl resonance for TML. The calculations involved fitting a variety of models for the complexation equilibria to the observed chemical shift data, which was measured as a function of solution conditions for each system, by using the nonlinear least-squares curve-fitting computer program KINET.[15] Estimates of both the formation constant and the chemical shift for each of the TML-containing complexes in the model were obtained from the calculations. The procedure has been described in detail previously.[16]

In each case, the simplest model considered to give a good fit to the experimental data was chosen as the best-fit model. The criteria used to judge the quality of the fit included (i) the level of agreement between the experimental chemical shift data and that predicted by the model and the parameters from the nonlinear least-squares calculation, (ii) the magnitude of the computer-estimated relative standard deviations for the formation constants and chemical shifts of all the species included in the model, and (iii) the relative concentrations of the various complexed species in the model. Complexes whose concentration, as calculated from the computer-estimated formation constants, were less than 1% of the total TML concentration over the entire pH region studied, were not considered to be significant for the experimental conditions used in this work, and were not included in the best-fit model.

Results

The focus of this study is on the complexation of TML by the sulfhydryl group of sulfhydryl-containing amino acids. Because such ligands contain several other potential coordination sites, the first step in this study was to assess the relative strengths of their complexation of TML. Mercaptoethanol was chosen as a model ligand with which to characterize binding by the sulfhydryl group, and glycine was chosen as a model ligand for amino acid carboxylate and amino group binding.

TML Complexes of Mercaptoethanol. The binding of TML by mercaptoethanol was studied by monitoring the chemical shift of the methyl protons of TML as a function of pH for solutions having constant TML to mercaptoethanol ratios and as a function of the TML to mercaptoethanol ratio at constant pH. In Figure 1 are presented chemical shift data for three solutions having different TML to ligand ratios (curves A–C) and also for TML in solution to which no coordinating ligand other than hyroxide has been added (curve D). Curve D is pH dependent because of the reaction of TML cation with hydroxide ion as described by eq 1 and 2. The equilibrium

$$(CH_3)_3Pb^+ + OH^- \rightleftarrows (CH_3)_3PbOH \quad (1)$$

$$(CH)_3Pb^+ + (CH_3)_3PbOH \rightleftarrows ((CH_3)_3Pb)_2OH^+ \quad (2)$$

constants for eq 1 and 2 are 7.34×10^4 and 31.2 M^{-1}, respectively.[12]

Curves A–C are different from curve D over the pH range ~4–13, indicating complexation of TML by mercaptoethanol. At the extremes of pH, they approach curve D; at low pH the complex is dissociated due to competition of protons with TML for mercaptoethanol while at high pH the complex is dissociated due to the formation of TMLOH. The chemical shift plateaus indicate maximum complexation over intermediate-pH regions where the concentrations of both competing ions are low.

To determine the stoichiometry of the TML–mercaptoethanol complexes, a mole ratio experiment was performed in which the TML chemical shift was measured as a function of the mercaptoethanol to TML ratio at pH 8.0 (Figure 2). These data indicate the formation of a complex having a ligand to TML ratio of 1 and little if any complex having a ratio greater than 1. At ratios less than 1, there is a slight curvature suggesting complexes which have a TML to ligand ratio greater than 1; as described below, analysis of the data in Figure 1 indicates the formation of a complex of the stoichiometry $(TML)_2SR^+$.

For the TML–mercaptoethanol system and for all the other systems studied in this work, exchange of TML between its various complexed and free forms is rapid on the NMR time scale. Formation constants for the complexes were determined from the chemical shifts of the exchange-averaged TML

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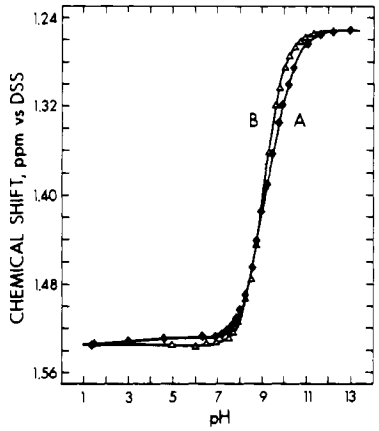

Figure 3. pH dependence of the chemical shift of TML in solutions containing (A) 0.0100 M TML and 0.100 M glycine and (B) 0.0100 M TML (0.3 M ionic strength and 25 °C).

resonance, which for a given solution is the average of the chemical shifts of the various TML species present in solution, weighted according to their relative populations. Formation constants and chemical shifts for the various TML complexes were calculated by fitting various models for the complexation equilibria to the observed chemical shift data, by using the nonlinear least-squares curve-fitting computer program KINET;[15] the procedure has been described in detail previously.[16] The best fit to the experimental data for the TML–mercaptoethanol system was obtained for a model which included both one-to-one and two-to-one TML-to-mercaptoethanol complexes (eq 3–6), where RS^- represents the sulfhydryl-deprotonated form of mercaptoethanol. This model gave a considerably better fit to the experimental data than one which included just a one-to-one TML-to-mercaptoethanol complex. A model containing a one-to-two TML-to-mercaptoethanol complex was not considered on the basis of the results of the mole ratio study in Figure 2.

$$TML^+ + RS^- \rightleftarrows TMLSR \quad (3)$$

$$K_{fS} = \frac{[TMLSR]}{[TML^+][RS^-]} \quad (4)$$

$$TML^+ + TMLSR \rightleftarrows (TML)_2SR^+ \quad (5)$$

$$K_{fD} = \frac{[(TML)_2SR^+]}{[TML^+][TMLSR]} \quad (6)$$

The formation constants and chemical shifts calculated for the complexes with all the data in curves A–C in Figure 1 simultaneously are listed in Table I. A pK_A of 9.62 for mercaptoethanol was used in these calculations; this value was determined by ^1H NMR at an ionic strength of 0.3 M. No literature values are available for comparison with these formation constants; however, the close agreement between the observed data and the calculated curves (Figure 1) supports the validity of the results. The large relative error reported for K_{fD} is due to the concentration of $(TML)_2SR^+$ always being a small fraction of the total TML, and thus K_{fD} cannot be measured with a high degree of precision.

TML Complexes of Glycine. Chemical shift data for TML in a solution containing glycine and TML at a ten-to-one ratio are shown in Figure 3. The different chemical shift behavior as compared to that for TML alone indicates complexation; however, the small difference, considering the large glycine to TML ratio, suggests that the extent of complexation is small. Formation constants were determined from the chemical shift data by nonlinear least-squares calculations by using KINET;[15] the model which resulted in the best fit to the data involves complexation of TML by the zwitterionic ($HL^\pm$) and fully deprotonated forms of glycine (eq 7 and 8). The constants

$$TML^+ + HL^\pm \overset{K_{f1}}{\rightleftharpoons} TML{\cdot}LH^+ \quad (7)$$

$$TML^+ + L^- \overset{K_{f2}}{\rightleftharpoons} TML{\cdot}L \quad (8)$$

are reported in Table I. The relatively large uncertainties associated with the formation constants are due to the small extent to which the TML is complexed by glycine; competitive equilibria involving ligand protonation and reaction of hydroxide with TML preclude the formation of appreciable amounts of the glycine complex over most of the pH range. A model which included only the complex $TML{\cdot}LH^+$ did not give a good fit to the data at pH >9, and a model which included only the complex TML·L did not give a good fit to the data at pH <9.

The small value of K_{f2} for glycine relative to K_{fS} for mercaptoethanol allows us to simplify the models considered for the complexation of TML by sulfhydryl-containing amino acids. In sulfhydryl-containing amino acids, the amino and sulfhydryl groups ionize and thus become available for complexation, more or less simultaneously. However, on the basis of the negligible value for K_{f2} relative to K_{fS}, complexation by the glycine-like moiety has been neglected in the models used for solutions having low TML to sulfhydryl-containing amino acid ratios. Also, since $K_{fS} \gg K_{fD}$ and the ligand to TML ratios used in the following studies were greater than 1, com-

Table I. Formation Constants and Chemical Shifts of $(CH_3)_3Pb^{IV}$ Complexes[a,b]

ligand	donor atom	const	value of const, M^{-1}	chem shift[c]
OH^-	O	K_1	7.3×10^4	1.253[d]
$(CH_3)_3PbOH$	O	K_2	31.2	1.327[d]
$HOCH_2CH_2S^-$	S	K_{fS}	$(9.05 \pm 0.11) \times 10^5$	1.325 ± 0.001
$HOCH_2CH_2SPb(CH_3)_3$	S	K_{fD}	14.0 ± 8.8	1.454 ± 0.007
$H_3N^+CH_2CO_2^-$	O	K_{f1}	1.26 ± 0.58	1.481 ± 0.020
$H_2NCH_2CO_2^-$	O	K_{f2}	29.5 ± 3.8	1.433 ± 0.016
$CH_3CONHCH(C(CH_3)_2SH)CO_2^-$	O	K_{fO}	4.0 ± 2.1	1.465 ± 0.030
$CH_3CONHCH(C(CH_3)_2S^-)CO_2^-$	S	K_{fS}	$(4.07 \pm 0.21) \times 10^5$	1.351 ± 0.001
$H_3N^+CH(C(CH_3)_2S^-)CO_2^-$	S	K_{f1S}	$(1.13 \pm 0.05) \times 10^4$	1.414 ± 0.001
$H_2NCH(C(CH_3)_2S^-)CO_2^-$	S	K_{f2S}	$(4.22 \pm 0.32) \times 10^5$	1.373 ± 0.001
$H_3N^+CH(CH_2SH)CO_2^-$	O	K_{fO}	2.2 ± 2.0	1.426 ± 0.089
$H_3N^+CH(CH_2S^-)CO_2^-$	S	K_{f1S}	$(9.67 \pm 0.27) \times 10^4$	1.356 ± 0.001
$H_2NCH(CH_2S^-)CO_2^-$	S	K_{f2S}	$(9.24 \pm 0.50) \times 10^5$	1.325 ± 0.001

[a] At 25 °C and 0.3 M ionic strength. [b] Errors are linear estimates of the standard deviation.[15] [c] ppm vs. DSS. [d] Reference 12.

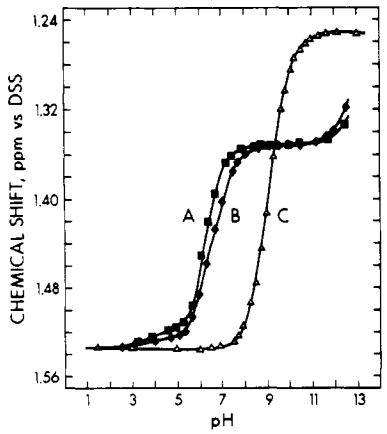

Figure 4. pH dependence of the chemical shift of TML in solutions containing (A) 0.0100 M TML and 0.0395 M *N*-acetyl-D,L-penicillamine, (B) 0.0100 M TML and 0.0198 M *N*-acetyl-D,L-penicillamine, and (C) 0.0100 M TML (0.3 M ionic strength and 25 °C).

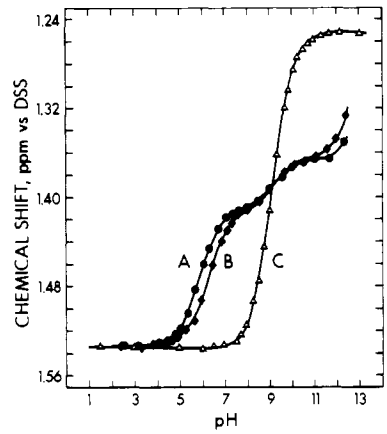

Figure 5. pH dependence of the chemical shift of TML in solutions containing (A) 0.00500 M TML and 0.0199 M D,L-penicillamine, (B) 0.00998 M TML and 0.00996 M D,L-penicillamine, and (C) 0.0100 M TML (0.3 M ionic strength and 25 °C).

plexes with two TML ions complexed to a sulfur were not detected for the three ligands considered below.

TML Complexes of *N*-Acetyl-D,L-penicillamine. Chemical shift data for TML in solutions containing *N*-acetyl-D,L-penicillamine (AP) and TML at two-to-one and four-to-one ratios are shown in Figure 4. Comparison with Figure 1 indicates complexation of TML by AP to be similar to that by mercaptoethanol, with the exception of different complexation behavior at pH <5. The model found to best fit the TML chemical shift data involves complexation of TML by the carboxylate group at pH <5 with the sulfhydryl group protonated; at pH >5, the majority of the TML is complexed by the deprotonated sulfhydryl group. The formation constants for these complexes, represented by K_{fO} and K_{fS}, respectively, are listed in Table I. Acid dissociation constants of pK_{a1} = 3.48 and pK_{a2} = 10.28 were used in the calculation of the formation constants; these values were determined by potentiometric titration in 0.3 M $NaClO_4$ at 25 °C.

TML Complexes of Penicillamine. Chemical shift data for TML in solutions containing penicillamine (P) and TML are shown in Figure 5. In contrast to the plateaus observed over the intermediate pH regions in Figures 1 and 4, the chemical shift changes continuously in Figure 5. This different behavior is due to the more complicated acid–base chemistry of D,L-penicillamine.[17] Specifically, the sulfhydryl and ammonium

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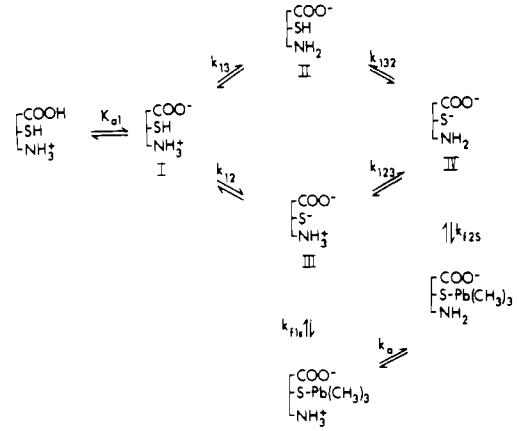
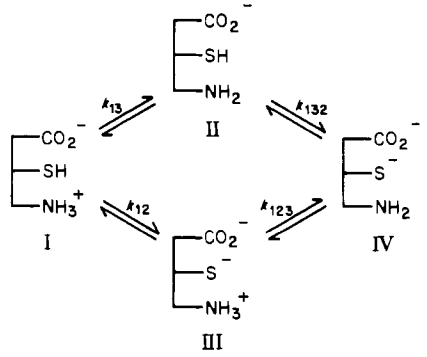


Figure 6. Microscopic acid–base and complexation equilibria of penicillamine in solutions containing trimethyllead.

Scheme I



groups are titrated over the same pH range as described by the microscopic Scheme I, where k_{12}, etc. are microscopic acid dissociation constants. The last digit of a subscript refers to the group dissociating in that step, and the preceding digits identify groups dissociated in previous steps; the subscripts 1–3 refer to the carboxylate, sulfhydryl, and amino groups, respectively. The values used for the microscopic constants are pk_{12} = 8.03, pk_{13} = 8.61, pk_{123} = 10.29, and pk_{132} = 9.70; these values were calculated for 25 °C and 0.3 M ionic strength from those reported by Martin and Wilson[17] for 25 °C and 0.16 M ionic strength by using the modified Davies equation.[18-20] The important point is that the acid dissociation constant for the sulfhydryl group changes when the ammonium group dissociates; thus the extent of complexation of TML by forms III and IV is different, giving rise to the chemical shift behavior in Figure 5.

The best fit to the chemical shift data was obtained with the microscopic complexation scheme shown in Figure 6. This model considers complexation only by forms III and IV, as described by eq 9 and 10, where the subscripts with HP_{12}^-

$$HP_{12}^- + TML \rightleftharpoons TML{\cdot}PH \qquad (9)$$

$$P^{2-} + TML \rightleftharpoons TML{\cdot}P^- \qquad (10)$$

indicate species III in the microscheme. The formation constants and chemical shifts of the complexes are listed in Table I. A model was also tried in which a TML–carboxylate complex involving species I in the microscheme was included; however, no constant could be derived for such a complex.

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TML Complexes of Cysteine. Chemical shift data for TML in solutions containing TML and cysteine are similar to those in Figure 5 for penicillamine, with the exception that complexation extends to a lower pH (~3). The chemical shift of TML changes continuously over the intermediate pH range as in Figure 5 because, as with penicillamine, the sulfhydryl and ammonium groups deprotonate over the same pH range. At the molecular level, their acid–base chemistry is described by the same microscheme as for penicillamine. For the conditions used in this work (25 °C and 0.3 M ionic strength), the microconstants were calculated from the constants reported by Coates, Marsden, and Rigg to be $pk_{12} = 8.38$, $pk_{13} = 8.73$, $pk_{123} = 10.09$, and $pk_{132} = 9.74$.[21] The pK for the carboxylate group is 1.93 for these conditions.[22] The model for the complexation of TML which gave the best fit to the data was identical with that for penicillamine with the exception that it includes a complex in which TML binds to the carboxylate group of species I in the microscheme in Figure 6. As mentioned above, the chemical shift data indicates complexation at lower pH values than with penicillamine. The values for the formation constants and chemical shifts of the complexes are listed in Table I. The large error estimates for the formation constant for the carboxylate complex result from the low concentrations of the complex.

Discussion

The coordination geometry around the lead of $(CH_3)_3Pb^{IV}$ in strong donor solvents is thought to be trigonal bipyramidal, with the three methyl groups and the lead in the trigonal unit and two solvent molecules in axial positions.[23] Complexes form by ligand substitution of axial solvent molecules. The results in Figure 2 indicate that complexes having ligand to TML ratios greater than 1 do not form with the sulfhydryl donor, at least in aqueous solutions having ligand to TML ratios up to 6.

If the two water molecules of aqueous $(CH_3)_3Pb^{IV}$ are in trans positions, chelation in TML complexes of ligands such as glycine, penicillamine, and cysteine is prevented by the equatorial methyl groups. The small differences between K_{f1} and K_{f2} for the TML–glycine complexes and between K_{f1s} and K_{f2s} for both the TML–penicillamine and the TML–cysteine complexes are consistent with monodentate coordination of these three ligands to TML, even when the ammonium group is deprotonated. The difference between the two constants in each pair is probably due to increased basicity of the deprotonated sulfhydryl group when the ammonium group is deprotonated; an increase in log K_f with increasing ligand pK_a has been observed for TML–carboxylate complexes,[12] and a general correlation of this type is well established for methylmercury complexes.[1]

A variety of ligands was selected for the present work to make possible the study of the effects of various ligand parameters on the formation of TML complexes. The results demonstrate that carboxylate, sulfhydryl, and TML-complexed sulfhydryl groups are all potential binding sites for TML and that, of the various ligand types studied to date,[12,16] the deprotonated sulfhydryl group forms complexes with the largest formation constants. However, even though the formation constants are large, the amount of complexation by the sulfhydryl group can be small because of its acid–base chemistry

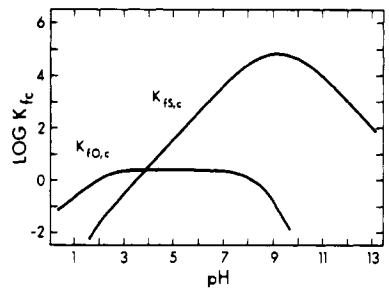

Figure 7. Conditional formation constants of the *N*-acetyl-D,L-penicillamine complexes of TML as a function of pH.

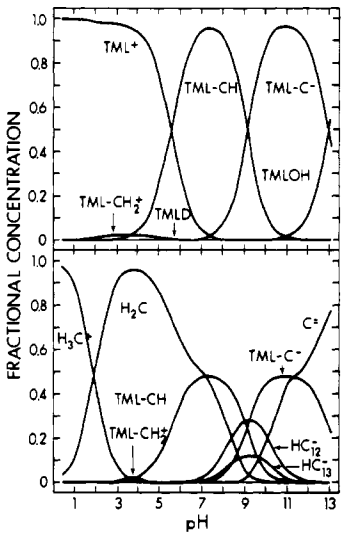

Figure 8. pH dependence of the TML-containing (upper plot) and cysteine-containing (lower plot) species distribution in a solution containing 0.005 M TML and 0.010 M cysteine. H_3C^+, H_2C, HC, and C represent the fully protonated through the fully deprotonated forms of cysteine; HC_{13}^- and HC_{12}^- represent species II and III in the microscheme for cysteine corresponding to Figure 6.

and that of the TML cation. Similarly, the amount of complexation by the carboxylate group is strongly pH dependent. The pH dependence of the binding, and thus the extent of complexation by the various groups, can be most easily characterized in terms of conditional formation constants, K_{fc}, defined as

$$[TML]_f + [Lig]_f \overset{K_{fc}}{\rightleftharpoons} [TML{\cdot}Lig]_{tot}$$

where $[TML]_f$ and $[Lig]_f$ include all free forms of TML and ligand and $[TML{\cdot}Lig]_{tot}$ includes all forms (e.g., amino protonated and deprotonated) of the particular complex under study. K_{fc} values for the carboxyl and sulfhydryl complexes of cysteine are presented as a function of pH in Figure 7. These conditional constants indicate that the sulfhydryl group is the favored binding site over the pH range 4–13. At lower pH, the carboxylate group becomes the favored binding site because of relatively less competition from the proton for the carboxylate group. At very low pH, little complexation occurs. At high pH, there is some dissociation of the sulfhydryl complex due to formation of the hydroxyl complex of TML. The distribution of TML among its various forms in a two-to-one cysteine–TML solution is shown as a function of pH in Figure 8. Also shown are the fractional concentrations of the various forms of cysteine in this solution as a function of pH.

With the microscopic formation constants for complexation of TML by the deprotonated sulfhydryl groups of cysteine and penicillamine when the ammonium group is protonated (K_{f1s}) and deprotonated (K_{f2s}), acid dissociation constants (k_a in Figure 6) can be calculated for the ammonium groups in these

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complexes. pk_a is calculated to be 9.11 and 8.71 for the TML-cysteine and TML-penicillamine complexes, respectively. These constants are both similar in magnitude to the microconstant pk_{13} for cysteine and penicillamine, suggesting that the TML cation complexed to the sulfhydryl group closely mimics a similarly bonded hydrogen ion, in terms of its effect on the acid strength of the neighboring ammonium groups.

Because of the one-coordinate nature of TML, chemotherapeutic ligands which are successful for the treatment of inorganic lead poisoning are not necessarily going to be effective for treating trialkyllead poisoning. For example, penicillamine is an effective treatment in inorganic lead poisoning; however, it was found to have little effect on intoxication due to trialkyllead compounds.[3] On the assumption that the ligand must form a complex with the trialkyllead species to be an effective treatment, this is as would be predicted from the results of this study; the conditional formation constants for the TML-cysteine and TML-glutathione[24] complexes at pH 7 are 3.8×10^3 and 3.6×10^3 as compared to 1.2×10^3 for the TML-penicillamine complex.

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Registry No. TML, 14570-16-2; cysteine, 52-90-4; penicillamine, 52-66-4; glycine, 56-40-6; *N*-acetylpenicillamine, 59-53-0; mercaptoethanol, 75-08-1.

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L-Histidine Complexes of Chromium(III)

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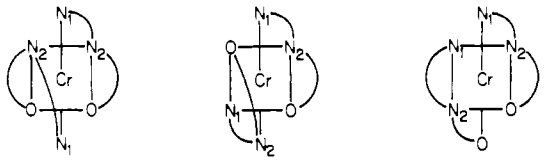
Two isomers of bis(L-histidinato)chromium(III), in which histidine functions as a tridentate ligand, have been prepared and characterized. In addition, a partially characterized di-μ-hydroxy-bis(L-histidinato)dichromium(III) complex is described. A simple angular overlap model calculation on the electronic spectra of the two $[Cr(L\text{-his})_2]^+$ isomers, together with data from another amino acid complex, yields values for the ligand field splitting parameter Δ (or $10Dq$) of 22.7×10^3, 21.1×10^3, and 17.1×10^3 cm^{-1} for the amine, imidazole (N^3), and carboxylate ligands, respectively. The sharp-line luminescence of the trans(imidazole) isomer of $[Cr(L\text{-his})_2]^+$ is also reported.

Introduction

Complexes of L-histidine with a wide variety of metal ions have been characterized. In bis complexes, histidinate often functions as a tridentate ligand[1-7] but, as with certain Cu(II) and Pt(II) complexes, may be bidentate, with the imidazole or carboxylate group uncoordinated.[8,9] A review article on transition-metal complexes with tridentate amino acids appeared in 1975.[10]

There have been no reports of tris complexes, in which histidine would presumably be bidentate, but bidentate coordination may be exhibited in binuclear complexes, some of which are of interest as oxygen carriers.[11]

An octahedral bis complex with tridentate L-histidine, in which each histidine coordinates facially, can assume three isomeric forms



trans(imidazole) trans(carboxylate) trans(amine)

(here N_1 represents imidazole, N_2 amine, and O carboxylate). The trans(imidazole) isomer appears to be favored among the first-row divalent cations whose crystal structures have been determined,[1-3,7] although both Zn(II) and Cd(II) form very distorted complexes, so that the orthoaxial representations above are inappropriate. All three isomers with Co(III) have been characterized,[12-14] the trans(imidazole) being predominant in the synthesis.

References to Cr(III) complexes with histidine are scant, consisting of our own preliminary report[15] and a doctoral dissertation by Grouhi-Witte,[16] in which bis complexes were prepared in solution only. We report here the characterization of the trans(imidazole) and trans(carboxylate) isomers of $[Cr(L\text{-his})_2]^+$ and the partial characterization of a binuclear complex, $[Cr_2(L\text{-his})_4(OH)_2]$.

Experimental Section

***trans*(Imidazole)-[Cr(L-his)$_2$](NO$_3$).** To a solution of NaOH (8.0 g, 0.2 mol) in water (125 mL) was added L-histidine (31 g, 0.2 mol) and $Cr(NO_3)_3 \cdot 9H_2O$ (40 g, 0.1 mol). The solution was heated on a steam bath for 8 h, during which time a fine reddish violet precipitate formed and then disappeared. The volume was allowed to sink to 50 mL, and orange-red crystals began to deposit. After cooling and filtration, 7 g of product was obtained. This was recrystallized by dissolving in water (60 mL), evaporating to 25 mL, and refrigerating overnight. The crystals obtained (4 g) were washed with water and ethanol and air-dried. Anal. Calcd for $[Cr(C_6H_8N_3O_2)_2](NO_3)$: C, 34.1; H, 3.8; N, 23.2; Cr, 12.3. Found: C, 33.8; H, 4.1; N, 23.1; Cr, 12.3. The crystals were almost insoluble in ethanol, only slightly soluble in cold water, but quite soluble in warm water. Dissolved in water, it eluted as one band on a cation-exchange column (Dowex 50W-X8).

***trans*(Carboxylate)-[Cr(L-his)$_2$](ClO$_4$).** The mother liquor from the above synthesis could be separated into two isomers (plus one or

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