

Mercury Binding to the Chelation Therapy Agents DMSA and DMPS and the Rational Design of Custom Chelators for Mercury

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Clinical chelation therapy of mercury poisoning generally uses one or both of two drugs—*meso*-dimercaptosuccinic acid (DMSA) and dimercaptopropanesulfonic acid (DMPS), commercially sold as Chemet and Dimaval, respectively. We have used a combination of mercury L_{III}-edge X-ray absorption spectroscopy and density functional theory calculations to investigate the chemistry of interaction of mercuric ions with each of these chelation therapy drugs. We show that neither DMSA nor DMPS forms a true chelate complex with mercuric ions and that these drugs should be considered suboptimal for their clinical task of binding mercuric ions. We discuss the design criteria for a mercuric specific chelator molecule or “custom chelator”, which might form the basis for an improved clinical treatment.

Introduction

Mercury is among the most toxic heavy elements (1–3), and its compounds have been linked with a number of human health problems, including neurological problems (3), myocardial infarction (4), and a possible involvement in the development of some kinds of autism (5, 6). The treatment of mercury poisoning in humans generally involves the use of chelation therapy (7, 8). A chelator is a molecule that binds a metal or metalloid ion by at least two functional groups to form a stable ring complex known as a chelate. Chelation therapy is the clinical treatment by which heavy metals are removed from the body through binding to a chelation therapeutic drug to form a chelate, which is in most cases subsequently excreted in urine. Dimercaptosuccinic acid (DMSA) and dimercaptopropanesulfonic acid (DMPS) are commercially sold as Chemet and Dimaval, respectively, and have both been widely used in the chelation therapy of mercury and heavy metals (7–10). These chelation agents are vicinal dithiols related to the now outmoded British anti-Lewisite (BAL) 2,3-dimercaptopropanol (Figure 1a), which was developed as an antidote for the arsenical war gas Lewisite (chlorovinylarsinedichloride) (11). BAL suffers from the disadvantages of low water

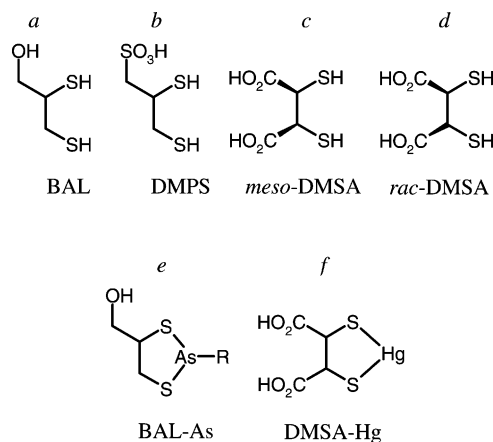


Figure 1. Structures of (a) BAL, (b) DMPS, (c) *meso*-DMSA, (d) *rac*-DMSA, (e) As³⁺ chelate with BAL, and (f) the structure previously proposed for DMSA chelate with Hg²⁺.

solubility and a noxious smell, and so, it was modified to produce DMPS (Figure 1b), which is water soluble and nearly odorless. DMSA (Figure 1c,d) was introduced later and has similar properties (i.e., excellent water solubility and no odor) with lower toxicity (7–10). The clinical use of DMSA differs from DMPS (and BAL) in that it is usually administered by mouth, whereas the others are generally given intravenously.

Trivalent arsenicals such as Lewisite kill by interacting with essential thiols, and in particular, the dithiol lipoic acid in enzymes such as pyruvate dehydrogenase (11). DMPS and DMSA are ideally suited for chelation therapy

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of As^{III} due to the stability of the five-membered rings formed upon chelation of arsenic (with a typical S–As–S bond angle of about 93°) (12) (Figure 1e), and it is widely believed that they bind a broad range of heavy metals with structures analogous to that shown for arsenic in Figure 1e (e.g., Figure 1f) (7). DMSA occurs in *rac* and *meso* diastereomers (Figure 1c,d, respectively), which apparently differ somewhat in their interaction with mercury (13, 14). Only the *meso* form is available commercially and used clinically; therefore, in what follows, DMSA is used to indicate the *meso* form, and we do not discuss the *rac* form further. To date, there have been no structural investigations of the interaction of Hg²⁺ with DMSA, DMPS, or BAL. We present herein a study of the solution chemistry of mercuric ions with DMSA and DMPS, employing X-ray absorption spectroscopy and density functional theory (DFT) calculations. Contrary to established thinking (e.g., 7), we show that the two functional groups of the chelator molecule cannot bind a common atom of mercury and that neither DMSA nor DMPS are well-optimized molecules for chelation therapy of mercury. It therefore seems very likely that there is room for significant improvement in clinical chelation therapy. Moreover, mercury in certain tissues (e.g., the brain) is known to be essentially impossible to remove using DMSA and DMPS [although this may be due to a lack of access to the brain, rather than the effectiveness (or lack of it) of DMSA and DMPS] (15). We lay out the major criteria for the rational design of metal specific or “custom chelators” and suggest directions for the development of potentially more effective drugs for mercury chelation therapy.

Materials and Methods

Sample Preparation. Reagents were purchased from Sigma Aldrich and were of the best quality available. Samples for X-ray absorption spectroscopy were prepared at 5 mM Hg (final) in 50 mM HEPES buffer, pH 7.0 (final), with 30% v/v glycerol glassing agent to prevent artifacts from ice crystals. To prevent the formation of precipitates, the Hg(NO₃)₂ was dissolved in a small quantity of dilute nitric acid prior to the addition of buffer. Appropriate quantities of buffered solutions of Hg(NO₃)₂, DMSA, and DMPS were added, incubated for 1 min at room temperature, and then loaded into 2 mm × 3 mm × 25 mm Lucite cuvettes frozen in liquid nitrogen immediately prior to data collection. Samples for chromatography were prepared in an identical manner but using 0.1 M bis-tris buffer (pH 7.0) and without the glycerol because the high viscosity of the glycerol solutions caused problems with the chromatography.

X-ray Absorption Spectroscopy. Measurements were carried out at the Stanford Synchrotron Radiation Laboratory with the SPEAR storage ring containing 60–100 mA at 3.0 GeV, on beamline 7-3 operating with a wiggler field 1.8 T, and using a Si(220) double crystal monochromator. Harmonic rejection was accomplished by detuning one monochromator crystal to 50% peak intensity. The incident X-ray intensity was monitored using a nitrogen-filled ionization chamber, and X-ray absorption was measured as the X-ray L_α fluorescence excitation spectrum using an array of 30 germanium intrinsic detectors (16). During data collection, the samples were maintained at a temperature of approximately 10 K using a liquid helium flow cryostat. For each sample, between four and six 35 min scans were accumulated, and the absorption of a standard Hg–Sn amalgam metal foil was measured simultaneously by transmittance. The energy was calibrated with reference to the lowest energy L_{III} inflection point of the metal foil, which was assumed to be 12285.0 eV. The spectrum of Hg–Sn amalgam was determined to be identical with that of a microparticulate aqueous suspen-

sion of pure metallic mercury precipitated from aqueous HgCl₂ by reduction with a slight excess of sodium borohydride.

The extended X-ray absorption fine structure (EXAFS) oscillations $\chi(k)$ were quantitatively analyzed by curve fitting using the EXAFSPAK suite of computer programs (17) as described by George et al. (18). Fourier transforms were phase-corrected for Hg–S backscattering. The threshold energy (E_0) was assumed to be 12305.0 eV, and ab initio theoretical phase and amplitude functions were calculated using the program FEFF version 8.2 (19, 20).

Size Exclusion Chromatography. Size exclusion chromatography in conjunction with inductively coupled plasma atomic emission spectroscopy (ICP-AES) was carried out as previously reported (21). A 1 cm × 30 cm Superdex Peptide column served as the stationary phase and was equipped with a Rheodyne Injector (50 μ L loop). All chromatography was carried out at room temperature using a mobile phase flow rate of 1 mL/min. Mercury was monitored at the 194.227 nm emission line (order 174) and sulfur at the 182.034 nm emission (order 185). The retention times of DMSA and blue dextran on the chromatographic system were 15.3 and 8.0 min, respectively, which defined the chromatographic window.

Molecular Modeling. DFT molecular modeling used the program Dmol³ Materials Studio Version 2.2 (22, 23). DFT is a rigorous yet convenient and practical method for computing structural details of metal coordination compounds and has been extensively validated. We expect bond length accuracies of better than 0.05 Å and good estimates of energetic trends between postulated molecular entities. The Becke exchange (24) and Perdew correlation (25) functionals were used to calculate both the potential during the self-consistent field procedure and the energy. Double numerical basis sets included polarization functions for all atoms. Calculations were spin-unrestricted, and all electron relativistic core potentials were used. No symmetry constraints were applied (unless otherwise stated), and optimized geometries used energy tolerances of 2.0×10^{-5} Hartree.

Results and Discussion

X-ray absorption spectra can be somewhat arbitrarily divided into two regions—the near-edge region, which is sensitive to electronic structure, and the EXAFS oscillations, which can be used to determine the details of local structure. Near-edge spectra provide a useful fingerprint of chemical type (26) but are difficult to interpret in quantitative molecular structural terms. EXAFS spectra, on the other hand, are relatively straightforward to interpret and provide accurate distances and identities of the nearby atoms. Figure 2 shows the results of titrating aqueous mercuric nitrate (approximating Hg²⁺ ions) with increasing amounts of the two chelators, DMSA and DMPS. Panels A and B show the Hg L_{III} near-edge spectra of samples with increasing DMSA (A) and DMPS (B). DMSA shows essentially identical near-edge spectra with chelator:Hg levels of 1:1 and higher. In contrast, DMPS shows gradual changes until chelator:Hg levels of 4:1 are achieved, indicating fundamental differences in solution chemistry. Nevertheless, the near-edge spectra of the two 1:1 mixtures are very similar.

Panels C and D of Figure 2 show the EXAFS Fourier transforms, phase-corrected for Hg–S backscattering, for the samples of panels A and B. All data were analyzed by quantitative curve fitting, and the numerical results are given in Table 1. Structurally characterized mercury compounds exhibit coordination numbers between two and eight (27). Examination of the Cambridge Structural Database indicates that most sulfur-bound mercury species are either two- or four-coordinate and these show typical Hg–S bond lengths of 2.35(1) and 2.55(3) Å,

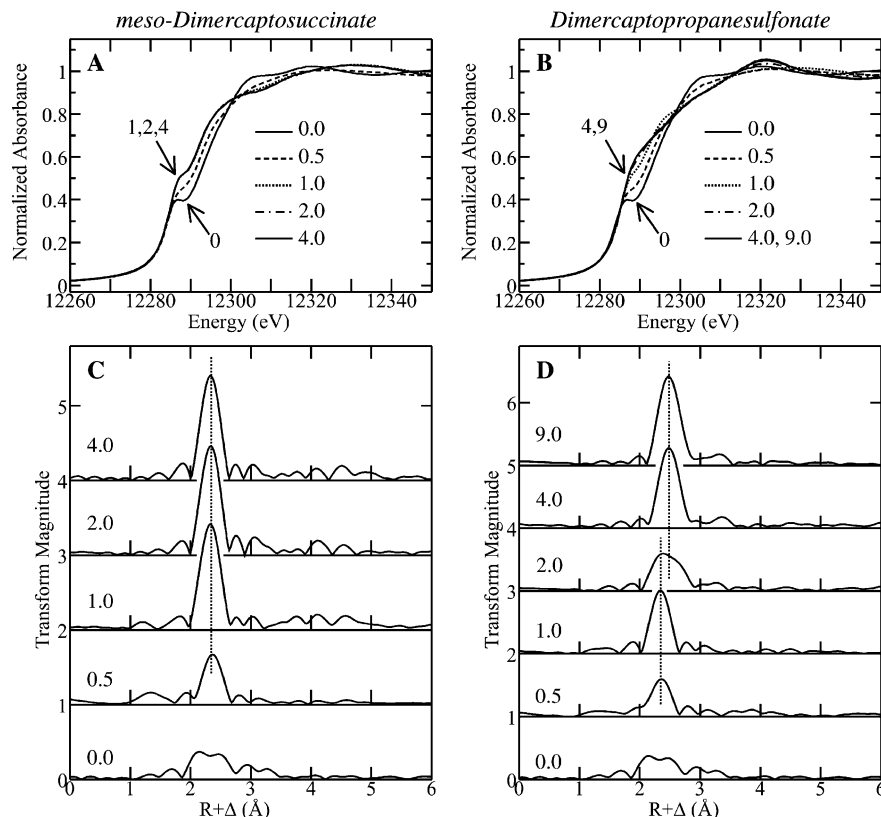


Figure 2. X-ray absorption spectroscopy titration of Hg^{2+} with DMSA and with DMPS. (A,B) The Hg L_{III} near-edge spectra; (C,D) the EXAFS Fourier transforms (phase-corrected for Hg–S backscattering). The ratios of DMSA: Hg^{2+} and DMPS: Hg^{2+} are indicated on the figure. The vertical broken lines in D show the expected peak positions for two- (lower) and four-coordinate mercury.

respectively. The two-coordinate species are always close to linear [S–Hg–S angle $177(4)^\circ$] while the four-coordinate species are approximately tetrahedral [S–Hg–S angle $110(2)^\circ$]. For DMSA:Hg of 1:1 and higher, the EXAFS clearly shows backscattering from two sulfur atoms at $2.345(1) \text{ \AA}$, consistent with a two-coordinate species. Similar results [two Hg–S at $2.367(2) \text{ \AA}$] are seen for DMPS:Hg of 1:1. Higher ratios (DMPS:Hg 4:1 and 9:1) give a Hg–S coordination number of 4 with an average bond length of $2.513(2) \text{ \AA}$, which is consistent with a four-coordinate geometry. Intermediate ratios (DMPS:Hg 2:1) give mixtures of two- and four-coordinate species. In agreement with this, principal component analyses of the sets of near-edge spectra shown in Figure 2A,B indicate that these can be explained as mixtures of only two and three components for DMSA and DMPS, respectively. Because the sulfurs in a single DMSA or DMPS molecule are not sufficiently separated to accommodate a linear two-coordinate S–Hg–S species, a true 1:1 complex such as that shown in Figure 1f would be impossibly strained. We therefore conclude that more complex structures must be occurring with at least two DMSA or DMPS molecules and at least two mercury atoms.

Size exclusion chromatography of the DMSA complexes (Figure 3) shows common column retention times of 13 min for sulfur and mercury using a DMSA:Hg ratio of 1:1. This suggests a single molecular entity, rather than a broad distribution of polymers, and EXAFS spectroscopy of a purified sample from this experiment gave identical data to that shown in Figure 2 (not illustrated). With higher levels of DMSA, the primary mercury species is the same as the DMSA:Hg ratio of 1:1, and unreacted DMSA is eluted with a column retention time of 15.3 min.

A small additional species with a column retention time of 11.8 min was also observed (Figure 3). As we will discuss below, the primary 13.0 min species is likely to be a binuclear species, formulated as $\text{Hg}_2(\text{DMSA})_2$, and the secondary 11.8 min species observed with higher DMSA:Hg ratios is very likely the trinuclear species $\text{Hg}_3(\text{DMSA})_3$. From the chromatography data, the simplest candidate molecule for the primary reaction product thus involves two DMSA molecules and two mercury atoms.

Density functional structural optimizations of the two possible diastereomers of $\text{Hg}_2(\text{DMSA})_2$ are shown in Figure 4. For each diastereomer, calculations were performed on the acids, anionic species, and anionic species with a single water associated with each carboxylate. These showed only very subtle structural differences, and only the anionic hydrated species is shown for each diastereomer (with water molecules omitted for clarity). The expected occurrence of two diastereomers in solution explains the absence of a clear Hg...Hg backscattering in the EXAFS Fourier transforms of Figure 2. The two diastereomers have different Hg...Hg distances, which result in near-cancellation of this interaction (Figure 5A). The curve-fitting analysis shown in Figure 5B includes all outer shell interactions (apart from hydrogens), including two different Hg...Hg distances, based on the results of density functional calculations shown in Figure 4. The excellent match between the calculated and the experimental curves adds more weight to the suggestion that the structures of Figure 4 are present in solution. Further density functional calculations (not illustrated) indicate that the ring-shaped trinuclear $\text{Hg}_3(\text{DMSA})_3$ is also expected to be a stable entity, with additional long ($\sim 3 \text{ \AA}$) Hg...S bonds involving adjacent DMSA sulfurs

Table 1. EXAFS Curve Fitting Results for Titrations of Hg²⁺ with DMSA and DMPS^a

drug	<i>n</i>	atom	<i>N</i>	<i>R</i>	σ^2	ΔE_0	<i>F</i>
DMSA	0 ^b	O	2	2.162(11)	0.0082(6)	-15.3(20)	0.504
	0.5	S	1	2.391(2)	0.0032(2)	-18.5(8)	0.384
		O	1	2.123(15)	0.0066(3)		
	1.0	S	2	2.344(2)	0.0028(1)	-18.0(6)	0.318 ^c
	2.0	S	2	2.346(2)	0.0025(1)	-17.5(6)	0.283
4.0	S	2	2.344(2)	0.0027(1)	-17.6(6)	0.259	
DMPS	0.5	S	1	2.384(2)	0.0039(1)	-18.3(8)	0.513
		O	1	2.127(15)	0.0089(4)		
	1.0	S	2	2.367(2)	0.0047(1)	-18.4(4)	0.242
	2.0	S	1.3(1)	2.397(5)	0.0047	-18.3(4)	0.439 ^d
		S	1.7(1)	2.528(6)	0.0059		
	4.0	S	4	2.514(2)	0.0066(1)	-17.8(5)	0.293
	9.0	S	4	2.514(2)	0.0059(1)	-18.2(5)	0.244

^a *n* is the mole ratio of drug (DMSA or DMPS) to Hg²⁺. Coordination numbers (*N*) and interatomic distances (*R*) are given in Å. Debye-Waller factors (σ^2 , the mean-square deviations in interatomic distance) are given in Å², and the threshold energy shifts (ΔE_0) are given in eV. The values in parentheses are the estimated SDs obtained from the diagonal elements of the covariance matrix. The fit error function *F* is defined as $[\sum k^6(\chi_{\text{calcd}} - \chi_{\text{expt}})^2 / \sum \chi_{\text{expt}}^2]^{1/2}$. ^b The presence of additional longer range Hg-O interactions is also indicated by the fits, specifically two Hg-O at 2.57(2) Å, ~one Hg-O at 2.74(2) Å, ~one Hg-O at 3.04(1) Å, and ~one Hg-O at 3.31(2) Å. The bond length for a purely digonal Hg-O coordination is 2.08 Å, and the 0.08 Å longer Hg-O bond length is consistent with longer distance oxygen ligation, which is common in mercury complexes (27). ^c The somewhat higher fit error in this case is mainly due to a slightly higher noise content in the spectrum. ^d The fit was achieved by fixing σ^2 at values obtained for the two-coordinate and four-coordinate species (*n* of 1 and 4, respectively) and refining the apparent coordination numbers *N*. This is necessary due to the high correlation between σ^2 and *N* in the refinement. The larger fit error reflects the poorer fit that was obtained with this method.

Table 2. Selected Bond Lengths (Å) and Angles (°) Computed for DMSA Hg²⁺ Complexes

	diastereomer 1	diastereomer 2
Hg-S	2.33, 2.38 2.38, 2.34	2.32, 2.31 2.33, 2.33
Hg...Hg	3.04	3.13
C-S-Hg	100.5, 113.5 113.5, 100.5	106.5, 110.7 113.9, 106.4
S-Hg-S	175.2, 174.4	168.2, 163.6

in conformers of both possible diastereomers. As we have discussed, the observed chromatography retention times (Figure 3) are also consistent with the primary product being the binuclear species (Figure 4).

As we have discussed above, DMPS forms a similar species with DMPS:Hg ratios of 1:1. The number of possible isomers (four conformers) is greater with DMPS than with DMSA because the carbon atom bearing the -CH₂SO₃⁻ moiety (Figure 1) is chiral, and commercially available DMPS is a racemic mixture of L- and D-forms. Figure 6a,b shows computed structures for two possible constitutional isomers; the other forms are similar with slightly differing Hg...Hg distances, as with DMSA. At higher DMPS:Hg ratios (e.g., 4:1), four-coordinate species are observed to form (Figure 6d). Density functional calculations indicate that true double chelate complexes, in which both thiolates of each of two DMPS molecules are bound to the metal (Figure 6c), ought to be stable. Indeed, a number of low molecular weight dithiolane double chelates have been characterized (28). However, the fact that exclusively four-coordinate species do not form at DMPS:Hg ratios lower than 4:1 indicates that significant quantities of true chelate complexes are not

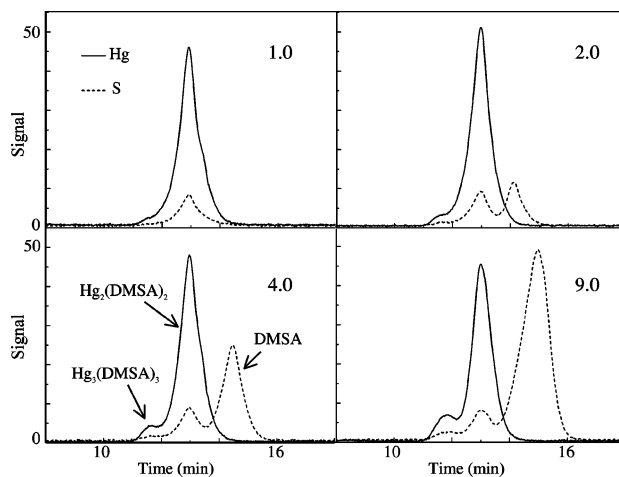


Figure 3. Size exclusion/ICP-AES chromatography of different DMSA:Hg²⁺ ratios. The DMSA:Hg²⁺ ratios are shown in the figure. The radii of spheres of equivalent volume to the computed electron density for the trinuclear Hg₃(DMSA)₃ and binuclear Hg₂(DMSA)₂ species and for free DMSA were approximately linearly related to the retention times (not illustrated) confirming the peak assignments to trinuclear and binuclear species.

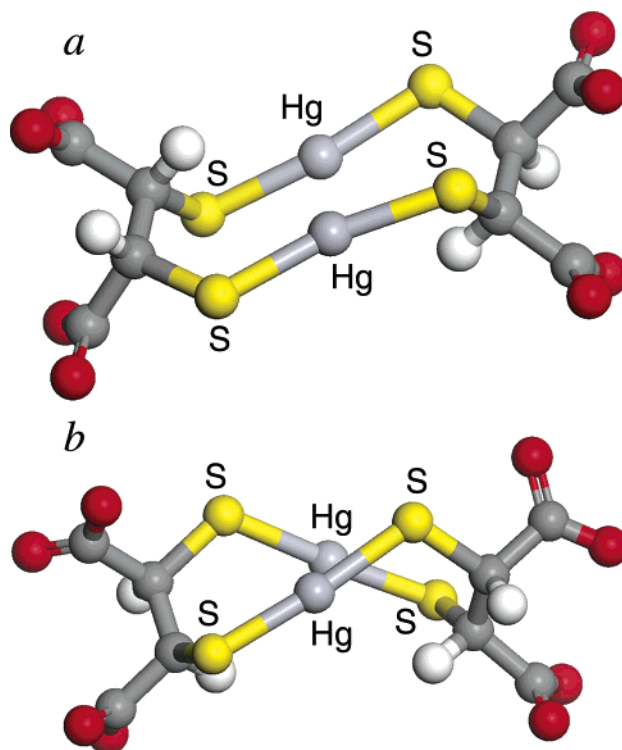


Figure 4. Calculated structures of the two diastereomers of the smallest possible DMSA:Hg²⁺ complex. The carbon atoms are depicted as dark gray; oxygen atoms are depicted as red; hydrogen atoms are depicted as light gray; and sulfur atoms are depicted as yellow.

formed in our experiments. In agreement with this, chromatography of a sample with Hg and excess DMPS (not illustrated) gives DMPS:Hg ratios of 4:1 for the coeluting sulfur and mercury peaks, suggesting structures related to the computed 4:1 species of Figure 6d.

We now address the question of why DMSA does not form a four-coordinate species as observed for DMPS. The most likely reason for this is that at the physiological pH used, the molecule would bear too large a negative charge to be stable. For example, a four-coordinate double

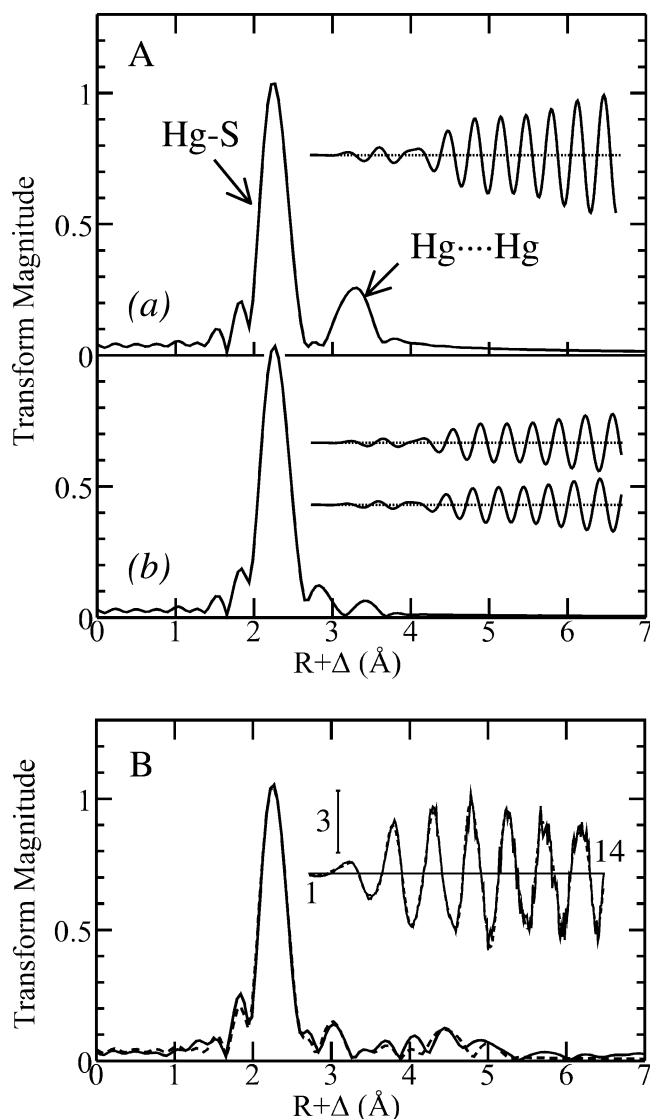


Figure 5. (A) Effects of dissimilar Hg...Hg distances computed for the two diastereomers, showing both the Fourier transform and the EXAFS oscillations (insets); graph a shows the expected EXAFS Fourier transform from one diastereomer including Hg-S and Hg...Hg interactions (the inset shows Hg...Hg EXAFS), and graph b shows the Fourier transform using the two different Hg...Hg interatomic distances computed for the two diastereomers (the inset shows how the two Hg...Hg EXAFS components cancel and is identically scaled to the inset in graph a). (B) EXAFS curve fitting analysis of the data of Figure 2 (DMSA:Hg²⁺ ratio of 1:1), showing Fourier transforms and total EXAFS oscillations (inset). The solid lines show the experimental data, and the broken lines show the computed curve using the best-fit Hg-S and the outer shell Hg...Hg and Hg...C distances computed using DFT.

chelate (one Hg, two DMSA) analogous to Figure 6c, would bear a charge of 6⁻, while the species with four DMSA molecules coordinating a single mercuric ion (as monofunctional reagents) analogous to Figure 6d would bear a massive negative charge of 14⁻. Furthermore, the negatively charged carboxylate groups are much closer to the coordinating thiolate group than is the sulfonate of DMPS, and this proximity would further destabilize the complex. In agreement with this, DFT calculations predict the stability of uncharged (protonated) but not of the charged species; in the charged case, the metal-ligand bonds dissociate during the geometry optimization. DMPS, on the other hand, which bears only a single negative charge, can form stable four-coordinate species,

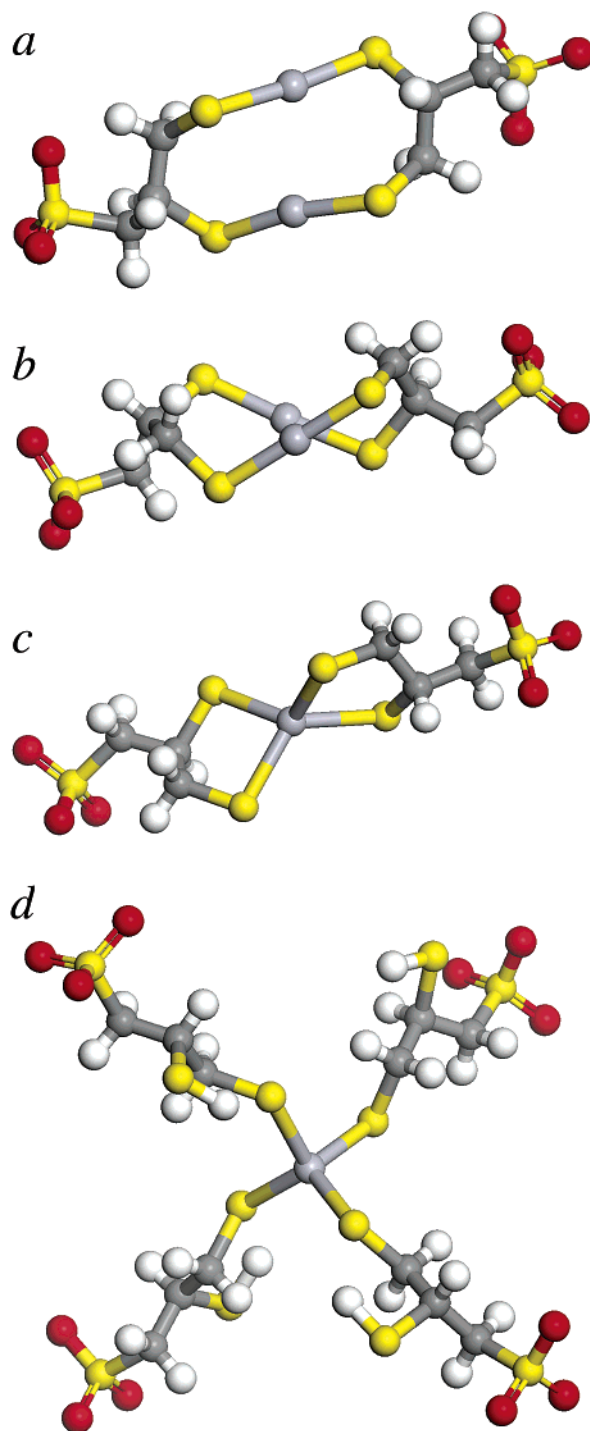


Figure 6. Calculated structures of possible Hg²⁺-DMPS complexes. Parts a and b show two of the four possible isomers for linear Hg coordination, part c shows the true double chelate, and part d shows the 4:1 complex detected by chromatography. The color scheme for the atoms is the same as that used in Figure 4.

and this is evident from both the experimental data (Figure 2) and the calculations (Figure 6).

One criterion for an effective drug for chelation therapy is that the chelator should interact in a stoichiometric manner with its target metal. In other words, if the chelation drug is exposed to the target metal ion in vivo, then it should be able to bind effectively all by itself, without the need for an additional molecular entity. We have shown that this criterion is not fulfilled by the clinically used mercury chelation therapeutic drugs,

DMSA and DMPS (Chemet and Dimaval). There is no doubt that DMSA and DMPS are effective, to some degree, in the clinical treatment of mercury poisoning (7–10, 29, 30), although not in all cases (31). Monomethyl mercury derivatives can form chelates, which are three-coordinate trigonal planar species; while very few three-coordinate mercury chelates have been characterized, at least one example has been reported (32). Nevertheless, we have presented strong evidence that these compounds are likely suboptimal for clinical chelation therapy by a considerable margin, and we expect that considerable improvements should be possible. We now consider the criteria for the rational design of a more effective agent for mercury chelation therapy. Quantum chemical methods can provide the criteria for the design of a drug that will not only bind mercuric ions with considerable tenacity but also with a high degree of specificity for mercuric ions above other cations—in effect a custom chelator.

As we have discussed above, one of the preferred coordinations of mercuric ions is a linear, two-coordinate geometry. A custom chelator optimized for such digonal coordination should present the metal with two thiol groups whose sulfurs are separated by twice the optimal Hg–S distance (i.e., $2 \times 2.345 \text{ \AA}$). We have used methyl mercury mercaptide ($\text{CH}_3\text{SHgSCH}_3$) as a minimal model to define the optimum binding geometry of Hg^{2+} to alkanethiolate donors. Figure 7 shows the calculated energy of this molecule as a function of Hg–S bond length, and of C–S–Hg and S–Hg–S bond angles. Our DFT calculations underestimate bond lengths by about 0.05 \AA [relative to test molecules of accurately known structure (27)], and slightly better absolute values for an ideal bond length can be derived from examination of the Cambridge Structural Database (27). Figure 7A shows a sharp minimum with an optimum bond length of 2.30 \AA , indicating that precise control of this parameter is required in a custom chelator, and the same is true of the C–S–Hg bond angle shown in Figure 7B, with an optimum of about 103° . In contrast, the S–Hg–S bond angle is rather less sensitive and can deviate by nearly 10° about the optimum of 180° with little energetic penalty. The energetic dependence of the C–SHgS–C torsion angle is shown in Figure 8, with a clear minimum at 90° . Less rigorous molecular modeling methods, such as molecular mechanics (MM2 or MM3) or semiempirical methods such as MOPAC (PM3 or PM5 Hamiltonians) or MND0d, predict structures with this angle closer to the more intuitive value of 180° with the methyl groups as far away from each other as possible. This illustrates the advantages of the more rigorous density functional method. Examination of the computed molecular orbitals shows that the highest occupied molecular orbital is made up of orthogonal S 3p with Hg 5d contributions (Figure 8), explaining the 90° torsion angle. Examination of linear S–Hg–S species in the Cambridge Structure Database (27) substantiates our conclusion of an approximately 90° torsion angle. In cases where the $\sim 90^\circ$ torsion angle is not observed, there are intermolecular bonding or other interactions within the extended solid that can explain this deviation.

The structure required for the immediate ligands to mercury in a custom chelator is thus well-defined. The next step is to design an organic molecule that can hold the thiol donors in the correct orientation and proximity. We have adopted a hybrid approach in which the sulfurs and adjacent carbon atoms were held rigid at their

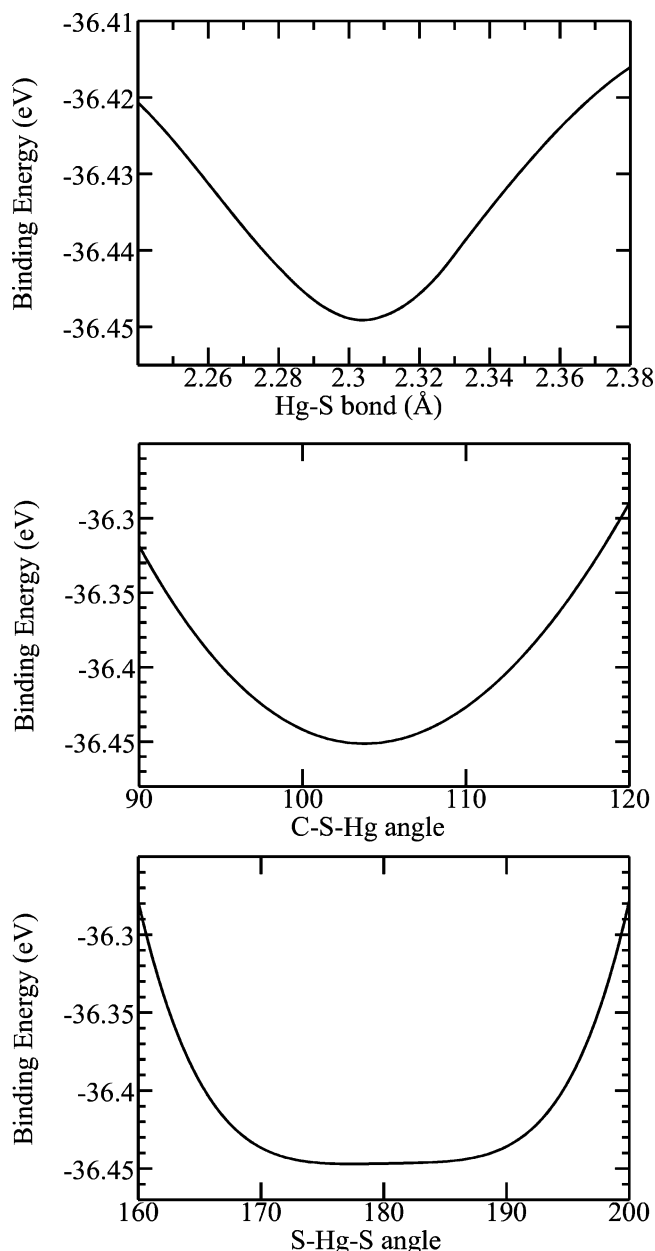


Figure 7. Calculated energy profile for Hg–S bond length, C–S–Hg bond angle, and S–Hg–S bond angle for bis-methylmercaptan-mercury(II). The binding energy of the ordinates is defined as the energy required to separate all atoms to infinity.

optimal positions and an organic framework was then refined using semiempirical methods (MOPAC 2002, employing a PM3 Hamiltonian), which have the advantage of better speed. The structure was adjusted by judicious addition of framework atoms such as carbon until it appeared strain free. The total structure was then refined, without restraints, using the density functional method and the Hg–S bond lengths and angles examined for signs of distortions. The calculated energy difference between the ligand and the metal-bound form was also examined as a crude index of stability. A large number of possible structures were generated using this approach, and the one shown in Figure 9 should be considered as only one possible candidate (and not a serious one at that). Additional functional groups can be added to adjust the compound's water solubility (e.g., carboxylates, sulfonates, etc.) and membrane-crossing

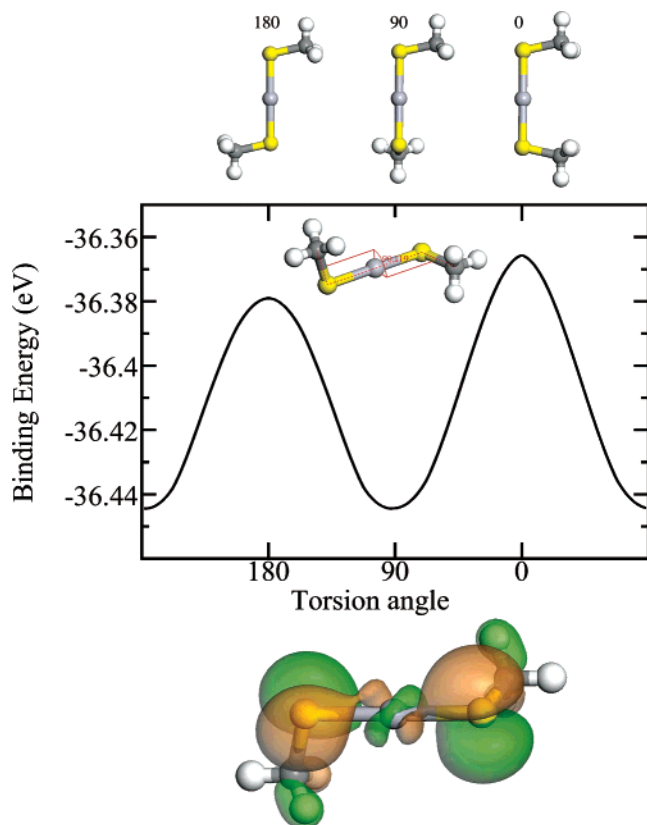


Figure 8. Calculated energy profile for the C–S–(Hg)–S–C torsion angle, showing the 90° minimum and the 0.03 Å² isosurface of the highest occupied molecular orbital.

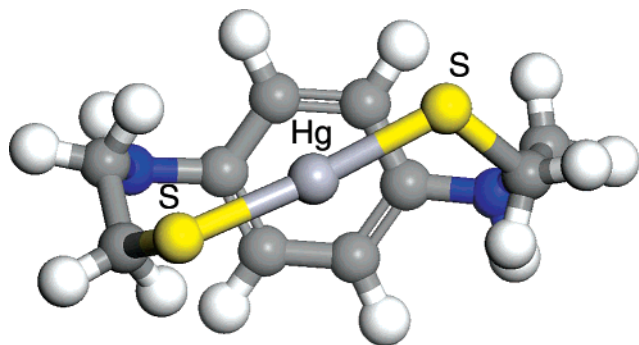


Figure 9. Structure of a possible custom chelator for Hg²⁺ based on digonal thiolate coordination (see text for details). Nitrogen atoms are shown in blue; otherwise, the color scheme is the same as for Figure 4. This chelator {2-[4-(2-mercaptoethylamino)phenyl amino]ethanethiol} is merely an example of the type of molecule that might be used and is not a serious candidate for a custom chelator. More optimal structures might incorporate thiols rigidly held in their ideal positions.

properties, although care must be taken not to interfere with the mercury binding parts of the molecule. We note that there are many additional factors in the design of an effective drug that we have not considered here, such as inherent toxicity of the custom chelator itself and how readily the chelate (once formed) is excreted. These factors mean that extensive studies upon the clinical effectiveness of any new drug will be required. However, as far as metal specificity is concerned, this will be primarily conferred from the coordination geometry and bond length. For example, numerous zinc thiolate species have been characterized, with a bond length of about 2.35 Å (i.e., about the same as the two-coordinate Hg–S bond

length) (27) but with a tetrahedral coordination geometry. On the other hand, cuprous ions readily adopt a digonal coordination geometry, but the Cu–S bond length of around 2.15 Å (27) means that the mercury custom chelator is too big to accommodate cuprous ions.

In summary, we have used X-ray absorption spectroscopy to show that the two clinically used mercury chelation therapeutic drugs, DMSA and DMPS (Chemet and Dimaval), cannot work as true chelators and are thus suboptimal for their clinical role by a considerable margin. We have also outlined the chemical factors that will be important in the design of a chelation therapeutic drug with specificity for mercuric ions, a custom chelator. Our approach could also be used to design therapeutic chelators for other elements, and of course, similar approaches could be used to design insoluble chelators to remove mercury and other elements from water and waste streams.

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