Published in final edited form as:

Polyhedron. 2013 November 12; 64: . doi:10.1016/j.poly.2013.05.012.

Structural characterization of 1,3-propanedithiols that feature carboxylic acids: Homologues of mercury chelating agents ☆

Wesley Sattler^a, Joshua H. Palmer^a, Christy C. Bridges^b, Lucy Joshee^b, Rudolfs K. Zalups^b, and Gerard Parkin^{a,*}

^aDepartment of Chemistry, Columbia University, New York, NY 10027, USA

^bDivision of Basic Medical Sciences, Mercer University School of Medicine, 1550 College St. Macon, GA 31207, USA

Abstract

The molecular structures of a series of 1,3-propanedithiols that contain carboxylic acid groups, namely *rac*- and *meso*-2,4-dimercaptoglutaric acid (H₄DMGA) and 2-carboxy-1,3-propanedithiol (H₃DMCP), have been determined by X-ray diffraction. Each compound exhibits two centrosymmetric intermolecular hydrogen bonding interactions between pairs of carboxylic acid groups, which result in a dimeric structure for H₃DMCP and a polymeric tape-like structure for *rac*- and *meso*-H₄DMGA. Significantly, the hydrogen bonding motifs observed for *rac*- and *meso*-H₄DMGA are very different to those observed for the 1,2-dithiol, *rac*-2,3-dimercaptosuccinic acid (*rac*-H₄DMSA), in which the two oxygen atoms of each carboxylic acid group hydrogen bond to two different carboxylic acid groups, thereby resulting in a hydrogen bonded sheet-like structure rather than a tape. Density functional theory calculations indicate that 1,3-dithiolate coordination to mercury results in larger S–Hg–S bond angles than does 1,2-dithiolate coordination, but these angles are far from linear. As such, ²-S₂ coordination of these dithiolate ligands is expected to be associated with mercury coordination numbers of greater than two. *In vivo* studies demonstrate that both *rac*-H₄DMGA and H₃DMCP reduce the renal burden of mercury in rats, although the compounds are not as effective as either 2,3-dimercaptopropane-1-sulfonic acid (H₃DMPS) or *meso*-H₄DMSA.

Keywords

Mercury; Thiolate; Chelating agent

1. Introduction

The primary aim of chelation therapy [1–3] is to rid vulnerable target sites in the body of toxic metals, such as mercury [4], following exposure. Previous compounds that have been utilized for chelation therapy include *meso*-2,3-dimercaptosuccinic acid (*meso*-H₄DMSA),¹ 2,3-dimercaptopropane-1-sulfonic acid (H₃DMPS), 2,3-dimercaptopropanol (British anti-lewisite; H₃BAL), and 2,3-dimercaptopropionic acid (H₃DMPA), as illustrated in Fig. 1. H₃DMPS and H₄DMSA are low molecular weight, water soluble, vicinal dithiols that have

☆Dedicated with respect to Professor George Christou on the occasion of his 60th birthday.

© 2013 Elsevier Ltd. All rights reserved.

*Corresponding author. parkin@columbia.edu (G. Parkin).

¹Dimercaptosuccinic acid is often given the abbreviation DMSA. However, here we use the abbreviation H₄DMSA in order to provide a distinction with the deprotonated derivatives.

proven to be effective in promoting urinary excretion of ionic forms of mercury and are used throughout the world to treat mercury intoxication [5,6]. It has been suggested, however, that these compounds are not ideal chelators for mercury and that the development of additional, more effective chelators is necessary [7]. Therefore, we sought to investigate other compounds that could serve as potential chelators of mercuric ions in biological systems.

From a chemical design point of view, an ideal chelating agent is, firstly, one that can gain rapid and efficient access to the intracellular milieu of target cells in the body that are at greatest risk of being adversely affected by the metal in question. Secondly, the chelating agent should be able to bind competitively and strongly to the toxic metal, which is likely to be coordinated to other intracellular molecules. Thirdly, the coordinating agent should not deplete intracellular stores of essential metals. In this regard, although H₄DMSA and H₃DMPS have the ability to promote rapid excretion of mercuric species, there is evidence that these dithiols may also bind to essential elements such as copper, chromium and zinc [1-3].

In addition to the above requirements, the metal complex formed should be able to serve as a substrate of membrane transporters that are capable of exporting or eliminating it from the target cells into an extracellular compartment to be excreted. In this regard, once internalized into the body, mercury species accumulate predominantly along the epithelial cells lining the proximal tubule in the kidneys, although other target cells in the body also accumulate and become intoxicated by mercury. The predilection for mercury species to be taken up so avidly along the renal proximal tubule relates to the activity of numerous membrane transporters present in both luminal and basolateral plasma membranes of these cells. Similarly, the ability of H₃DMPS and H₄DMSA to extract mercury from renal tissue relies on the ability of these agents to be taken up by carriers such as the organic anion transporters, OAT1 and OAT3, and the sodium dicarboxylate transporter, NaC3, present in the basolateral membrane of proximal tubular cells [5,8]. It has been hypothesized that once these coordinating agents gain access to cells *via* carriers on the basolateral membrane, they form complexes with intracellular mercury that are exported from the intracellular compartment into the tubular lumen for eventual excretion in urine [5].

Hence, since glutarate is an avid substrate of OAT1, OAT3, and NaC3 [5,8,9], an objective of the research described here was to investigate potential mercury coordinating agents that contain the glutarate motif. Specifically, it was hypothesized that incorporation of two thiols into glutaric acid could provide a potential means to deliver a dithiol binding moiety into one of the primary cellular targets of mercury species, namely the epithelial cells lining the renal proximal tubule. Therefore, we describe here an investigation of a series of 1,3-dithiols, namely *rac*- and *meso*-2,4-dimercaptoglutaric acid (H₄DMGA) and 2-carboxy-1,3-propanedithiol (H₃DMCP),² as illustrated in Fig. 2, which are homologues of mercury chelating agents that feature 1,2-dithiol moieties.

2. Results and discussion

In view of the well-known affinity of mercury for sulfur, as illustrated by the fact that mercury forms compounds with a diverse array of sulfur donor ligands (including thiolate [10-12], thioether [13] and thione [14,15] derivatives), much attention has been directed towards the use of sulfur-containing ligands in chelation therapy [1-3]. For example, a common feature of the chelating agents illustrated in Fig. 1 is the presence of a 1,2-dithiol

²The abbreviation H₃DMCP refers to the alternative name 1,3-dimercapto-2-carboxypropane. 2-Carboxy-1,3-propanedithiol is also referred to as 3-mercapto-2-(mercaptomethyl)propanoic acid and dihydroasparagusic acid.

moiety. Interestingly, despite the fact that these compounds are referred to as “chelating” agents, the modes by which these ligands bind to mercury have not been ascertained by X-ray diffraction, although several mercury derivatives of H₃BAL, H₃DMPS, and H₄DMSA have been investigated in solution [16]. In fact, mercury L_{III}-edge X-ray absorption spectroscopy has been used to provide evidence that neither H₃DMPS nor *meso*-H₄DMSA chelate to Hg²⁺, but rather bind in more complex ways involving mercury binding to more than one “chelating agent” ligand [7]. The ability of a dithiol ligand to form a stable chelate complex with a given metal center is, however, expected to be a function of both the length and geometry of the spacer between the thiol groups and also the other supporting ligands attached to the metal. Therefore, we report here an investigation of 1,3-dithiols that are structurally related to clinically useful mercury chelating agents. In particular, since carboxylic acid groups increase water solubility, attention is focused on H₃DMCP and H₄DMGA, which respectively contain one and two carboxylic acid groups (Fig. 2).

2.1. Molecular structures of 2,4-dimercaptoglutaric acid and 2-carboxy-1,3-propanedithiol

2,4-Dimercaptoglutaric acid (H₄DMGA) is structurally related to 2,3-dimercaptosuccinic acid (H₄DMSA) by the formal insertion of a methylene group. H₄DMGA exists as both *rac* and *meso* isomers and both forms were synthesized from 2,4-dibromoglutaric acid via a modification of the literature methods [17], as illustrated in Scheme 1. Specifically, rather than converting dimethyl-2,4-*bis*(acetylthio)glutarate to 1,2-dithiolane-3,5-dicarboxylic acid by a sequence involving treatment with (i) KOH(aq), (ii) NH₃(aq), (iii) I₂ and KI(aq), and (iv) HCl(aq), the conversion was achieved by refluxing with KHCO₃(aq) in air, followed by treatment with HCl(aq). The 1,2-dithiolane-3,5-dicarboxylic acids are separated by crystallization into the *rac* and *meso* diastereomers, from which the respective isomers of 2,4-dimercaptoglutaric acid are obtained by reduction with zinc in NaHCO₃(aq) followed by acidification.

The molecular structures of both *rac*- and *meso*-H₄DMGA have been determined by X-ray diffraction, as illustrated in Figs. 3 and 4. In each case, intermolecular O–H...O hydrogen bonding between pairs of carboxylic acid groups results in a polymeric array in the solid state (Figs. 5 and 6), with O...O distances of 2.647(2) and 2.610(2) Å for the *rac* isomer, and 2.706(2) and 2.611(2) Å for the *meso* isomer.

Interestingly, the structures of *rac*- and *meso*-H₄DMGA are quite distinct from those that have been reported for *rac*- and *meso*-H₄DMSA [18,19]. For example, rather than adopt a structure that features two hydrogen bonds between pairs of carboxylic acid groups, the two oxygen atoms of each carboxylic acid group of *rac*-H₄DMSA hydrogen bond to two *different* carboxylic acid groups [19]. As a result, rather than forming a hydrogen bonded tape, *rac*-H₄DMSA forms a hydrogen bonded sheet (Fig. 7).

In the case of *meso*-H₄DMSA, only the structure of the 1:2 *N,N*-dimethylformamide (DMF) adduct has been reported [18]. In contrast to the aforementioned structures, *meso*-H₄DMSA·2DMF does not possess hydrogen bonding interactions between pairs of carboxylic acid groups. Rather, each carboxylic acid group hydrogen bonds selectively to one DMF molecule, thereby resulting in a discrete [DMF–H₄DMSA–DMF] unit, as illustrated in Fig. 8 [20]. Each [DMF–H₄DMSA–DMF] moiety is, nevertheless, linked to two others *via* S–H...O interactions [*d*(S–H...O) = 2.48 Å; *d*(S...O) = 3.52 Å]³ [18,21] form an extended array; such S–H...O interactions are, however, weaker than O–H...O interactions [22].

³For comparison, the average S...O distance for structurally characterized compounds listed in the Cambridge Structural Database (Ref. [22]) is 3.208 Å, with a range of 2.88–3.32 Å.

In addition to the above dicarboxylic acid derivatives, we have also determined the molecular structure of a 1,3-propanedithiol that features only a single carboxylic acid group, namely 2-carboxy-1,3-propanedithiol (H_3DMCP) [23], which is a homologue of the chelating agent 2,3-dimercaptopropionic acid (H_3DMPA) [24]. However, in view of the fact that H_3DMCP contains only one carboxylic acid group, the compound exists as a centrosymmetric hydrogen bonded dimer (Fig. 9)⁴ rather than as a polymeric array of the type observed for *rac*- and *meso*- H_4DMGA (Fig. 5 and Fig. 6). Nevertheless, despite the fact that *rac*- H_4DMGA , *meso*- H_4DMGA and H_3DMCP possess different extended arrays, all three molecules have similar S–C–C–S torsion angles of approximately 120°, with a range of 116.2–126.0° (Table 1 and Fig. 10). Both the values and the narrow range of the torsion angles of these 1,3-dithiols provide a marked contrast with those of the 1,2-dithiols, *rac*- and *meso*- H_4DMSA , which exhibit torsion angles of 66.2° and 180°, respectively.

2.2. Influence of 1,2- versus 1,3-dithiolate substitution on S–Hg–S bond angles

In order to assess the impact of the spacer length on coordination of the above molecules to mercury, the molecular structures of a series of ²-*S,S* derivatives were evaluated by density functional theory calculations (Figs. 11 and 12).⁵ As expected for an increased spacer length [25], the S–Hg–S bond angles for the 1,3-derivatives are larger than those for the 1,2-derivatives, in various protonation states (Tables 2 and 3). The bond angles for the 1,3-derivatives are, however, far from linear, such that the molecules studied *in silico* are unlikely to correspond to stable species that would exist in solution [7]. These coordination geometries, therefore, suggest that the mercury centers in such species would be predisposed towards binding additional ligands [26]. In particular, the possibility of binding chloride is of specific relevance because the high concentration of chloride in blood plasma has prompted the suggestion that it is a ligand for Hg^{2+} in the body [27]. Therefore, the structures of chloride adducts $[\text{LHgCl}]^Q$ (Q = charge) were investigated computationally to evaluate the feasibility of coordinating Cl^- to the aforementioned LHg species.

Geometry optimization of the chloride adducts $[\text{LHgCl}]^Q$ results in structures with approximately trigonal planar geometries, as illustrated in Fig. 13 (selected bond lengths and angles are listed in Table 4). In this regard, well-defined, three-coordinate anionic mercury thiolate compounds are preceded [11,12,28], with the first structurally characterized mononuclear example, namely $[\text{Hg}(\text{SPh})_3]^-$, having been reported by Christou [11a]. Furthermore, the $[\text{HgS}_3]$ coordination environment is present in the MerR metalloregulatory protein [29]. In addition to *tris*(thiolate) compounds, three-coordinate anionic mercury thiolate compounds in which halides serve as co-ligands, as illustrated by $[(\text{PhS})_2\text{HgBr}]^-$, are also known [30,31]. Examination of the Cambridge Structural Database [21] indicates that the coordination geometries of planar, three-coordinate mercury compounds vary from T-shaped to Y-shaped, with a variety of bond angles. For example, the S–Hg–S bond angles in three-coordinate compounds range from at least 88.2° [32,33] to 176.9° [34]. Thus, the S–Hg–S angles computed for $[\text{LHgCl}]^Q$ are in accord with literature precedent. Of particular note, the S–Hg–S angles in $[\text{Hg}(\text{meso}-\text{H}_2\text{DMSA})\text{Cl}]^-$ (90.6°) and $[\text{Hg}(\text{rac}-\text{H}_2\text{DMSA})\text{Cl}]^-$ (89.3°) are very similar to the values for the three-coordinate centers in the 1,2-benzenedithiolate complex, $[\text{Hg}_2(\text{C}_6\text{H}_4\text{S}_2)_3]^{2-}$ (88.9° and 90.3°), which possesses 5-membered chelate rings [32,35,36]. Furthermore, the Hg–S and Hg–Cl bond lengths in the geometry optimized compounds (Table 4) are comparable to the respective mean values of 2.547 and 2.528 Å for structurally characterized compounds listed in the Cambridge Structural Database [21].

⁴The hydrogen bonded dimers are only weakly associated with other molecules *via* S–H···O interactions, with $d(\text{S} \cdots \text{O}) = 3.78$ Å.

⁵²-*S,O* and ²-*O,O* coordination modes were also considered but, in each case examined, the structure with the lowest energy corresponded to that with a ²-*S,S* coordination mode. Such observations are in accord with the so-called oxophilicity of mercury. See Ref. [13g].

2.3. Chelation studies

The ability of *rac*-H₄DMGA and H₃DMCP to extract mercuric ions from biological tissues was investigated by performing *in vivo* studies in rats. Interestingly, following injection of HgCl₂, treatment of rats with *rac*-H₄DMGA and H₃DMCP resulted in a reduction in the renal burden of mercury (Fig. 14). However, neither compound was as effective as either H₃DMPS or H₄DMSA (Fig. 14), which exhibited results similar to those observed in previous studies [37]. The lower efficacy of *rac*-H₄DMGA and H₃DMCP may be due to their inability to enter renal tubular cells *via* carriers in the basolateral plasma membrane or to the inability of export proteins on the apical plasma membrane of tubular epithelial cells (e.g. multidrug resistance associated protein, MRP2) to transport the mercury coordination compounds out of the cells. Another possible explanation for the lower efficacy of *rac*-H₄DMGA and H₃DMCP is that these molecules are more susceptible towards oxidation to their 1,2-dithiolanes [17a,23] than are H₃DMPS and H₄DMSA.

H₃DMCP was also able to reduce the burden of mercury in the liver, although *rac*-H₄DMGA was ineffective (Fig. 15A). As expected, treatment of rats with H₄DMSA or H₃DMPS resulted in a reduction of the hepatic burden of mercury (Fig. 15A). The hematologic burden of mercury was unchanged by H₃DMCP and actually increased following treatment with *rac*-H₄DMGA, suggesting that mercuric ions may be mobilized by the latter compound and secreted into blood (Fig. 15B). The distribution between plasma and cellular components of blood was altered significantly following treatment with either H₃DMCP or *rac*-H₄DMGA. Under control conditions using saline, mercury was distributed evenly between plasma and cells. Following treatment with H₃DMCP, the distribution of mercuric ions in blood shifted so that nearly 80% of the hematologic burden was associated with plasma. Interestingly, the hematologic distribution of mercury following treatment with *rac*-H₄DMGA was similar to that of H₃DMPS with approximately 35% in cells and 65% in plasma. The significance of these shifts in distribution is currently unknown. Treatment with H₄DMSA did not alter the distribution of mercuric ions in blood.

The amount of mercury in urine (Fig. 16A) was inversely related to the renal burden of mercury. For example, the saline-injected rats had the greatest renal burden of mercury, while the urine from this group of animals contained the least amount of mercury. Similar relationships were observed for all other treatment groups. The urinary content of mercury was significantly greater in each group of rats treated with a chelator than in those of the saline group. Treatment of rats with H₃DMPS resulted in the greatest excretion of mercury, with an efficacy similar to that induced by treatment with H₄DMSA. The urinary excretion of mercury following treatment of rats with H₃DMCP or *rac*-H₄DMGA was less than half of that for rats treated with H₃DMPS or H₄DMSA, and only treatment with H₃DMPS resulted in an increase in the content of mercury in feces (Fig. 16B). This pattern of elimination, in which the amount of mercury in feces and urine is greatest for rats treated with H₃DMPS, loosely reflects the measured content of mercury in hepatocytes (Fig. 15A).

It should be noted that when a high dose (100 mg per kg body weight delivered at 50 mg mL⁻¹) of H₃DMCP and *rac*-H₄DMGA was used, rats suffered from significant adverse effects including seizures and aggressive behavior. Reducing the dose of H₃DMCP and *rac*-H₄DMGA to 50 mg per kg body weight (delivered at 25 mg mL⁻¹), significantly reduced, but did not eliminate, unwanted side effects. The mechanisms underlying these effects are currently unknown.

3. Conclusions

In summary, the 1,3-dithiol-carboxylic acid compounds, *rac*-H₄DMGA, *meso*-H₄DMGA and H₃DMCP, all exhibit two centrosymmetric intermolecular hydrogen bonding

interactions between pairs of carboxylic acid groups. This hydrogen bonding pattern results in a dimeric structure for H₃DMCP and a polymeric tape-like structure for *rac*- and *meso*-H₄DMGA. In this regard, the tape-like hydrogen bonded array of *rac*- and *meso*-H₄DMGA stands in marked contrast to the sheet-like structure of the 1,2-dithiol counterpart, *meso*-H₄DMSA, which results from the two oxygen atoms of each carboxylic acid group hydrogen bonding to two different carboxylic acid groups. Density functional theory calculations on a series of mercury species that feature ²-S₂ coordination of these ligands indicate that 1,3-dithiolate coordination to mercury is accompanied by larger S–Hg–S bond angles than is 1,2-dithiolate coordination. However, the angles in the 1,3-dithiolate species are far from linear, such that ²-S₂ coordination of these ligands is expected to be associated with mercury coordination numbers of greater than two. *In vivo* studies demonstrate that both *rac*-H₄DMGA and H₃DMCP are capable of reducing the renal burden of mercury in rats that have been injected with HgCl₂, although the compounds are not as effective as either of the classical therapeutic agents, H₃DMPS and *meso*-H₄DMSA.

4. Experimental section

4.1. General considerations

All manipulations were performed in air unless stated otherwise. Solvents were purified and degassed by standard procedures. ¹H NMR spectra were measured on Bruker 300 DRX, Bruker 400 DRX, and Bruker Avance 500 DMX spectrometers. ¹H NMR chemical shifts are reported in ppm relative to SiMe₄ (= 0) and were referenced internally with respect to the protio solvent impurity (= 2.50 for *d*₆-acetone and 4.79 for D₂O) [38]. Coupling constants are given in hertz. All reagents were obtained from Aldrich, with the exception of potassium thioacetate, which was obtained from Acros Organics, and formic acid and hydrobromic acid, which were obtained from Fluka. 2,4-Dibromoglutaric acid [39] and 2-carboxy-1,3-propanedithiol [23a] were prepared by the literature methods, and crystals of the latter suitable for X-ray diffraction were obtained by cooling of a hexanes solution.

4.2. X-ray structure determinations

X-ray diffraction data were collected on a Bruker Apex II diffractometer. Crystal data, data collection and refinement parameters are summarized in Table 5. The structures were solved using direct methods and standard difference map techniques, and were refined by full-matrix least-squares procedures on *F*² with SHELXTL (Version 6.1) [40].

4.3. Synthesis of *rac*- and *meso*-2,4-dimercaptoglutaric acids

4.3.1. Dimethyl-2,4-dibromoglutarate—Dimethyl-2,4-dibromoglutarate [39] was synthesized by esterification of 2,4-dibromoglutaric acid. A solution of 2,4-dibromoglutaric acid (mixture of diastereomers, 10.3 g, 35.53 mmol) in methanol (*ca.* 70 mL) was treated with HCl (1.0 M in Et₂O, 10.0 mL, 10.0 mmol) and the mixture was stirred for 2 days at room temperature. After this period, the volatile components were removed *in vacuo* and the residue obtained was dissolved in Et₂O and washed with a saturated solution of NaHCO₃(aq). The organic layer was dried with MgSO₄, after which the mixture was filtered and the solvent removed *in vacuo* to give dimethyl 2,4-dibromoglutarate (9.77 g, 87%, *rac:meso* ratio 1.7:1). *Rac* isomer ¹H NMR (*d*₆-acetone): 2.72 [m, 2H, CH₂{(CHBr)(CO₂CH₃)}₂], 3.78 [s, 6H, CH₂{(CHBr)(CO₂CH₃)}₂], 4.59 [t, ³*J*_{H–H} = 7 Hz, 2H, CH₂{(CHBr)(CO₂CH₃)}₂]. *Meso* isomer ¹H NMR (*d*₆-acetone): 2.60 [m, 1H, CH₂{(CHBr)(CO₂CH₃)}₂], 2.95 [m, 1H, CH₂{(CHBr)(CO₂CH₃)}₂], 3.78 [s, 6H, CH₂{(CHBr)(CO₂CH₃)}₂], 4.54 [t, ³*J*_{H–H} = 7 Hz, 2H, CH₂{(CHBr)(CO₂CH₃)}₂].

4.3.2. Dimethyl-2,4-bis(acetylthio)glutarate—Dimethyl-2,4-bis(acetylthio)glutarate was prepared by a modification of the literature method [17]. A solution of potassium

thioacetate (11.85 g, 103.8 mmol) in methanol (*ca.* 50 mL) was added slowly to a solution of dimethyl-2,4-dibromoglutarate (15.28 g, 48.0 mmol) in methanol (*ca.* 50 mL) at 0 °C, thereby resulting in a color change from red to yellow, accompanied by precipitation of KBr. After the addition was complete, the reaction was allowed to warm to room temperature, and the mixture was stirred overnight. The mixture was filtered and the volatile components were removed from the filtrate *in vacuo*. The residue obtained was extracted into Et₂O and washed with H₂O. The organic layer was isolated and dried with MgSO₄, after which the volatile components were removed *in vacuo* to give dimethyl 2,4-bis(acetylthio)glutarate as a dark yellow oil (12.58 g, 85.0%) as a mixture of isomers of sufficient purity to be used directly for the synthesis of the 1,2-dithiolane-3,5-dicarboxylic acids (see below). ¹H NMR (*d*₆-acetone): *Meso*-isomer: 2.05 [m, 1H, CH₂{(CHSAc)(CO₂CH₃)}₂], 2.39 [s, 6H, CH₂{(CHSAc)(CO₂CH₃)}₂], 2.66 [m, 1H, CH₂{(CHSAc)(CO₂CH₃)}₂], 3.69 (overlap with *rac*-isomer) [s, 6H, CH₂{(CHSAc)(CO₂CH₃)}₂], 4.28 (overlap with *rac*-isomer) [m, 2H, CH₂{(CHSAc)(CO₂CH₃)}₂]; *rac*-isomer: 2.35 [s, 6H, CH₂{(CHSAc)(CO₂CH₃)}₂], 2.83 [s, 2H, CH₂{(CHSAc)(CO₂CH₃)}₂], 3.69 (overlap with *meso*-isomer) [s, 6H, CH₂{(CHSAc)(CO₂CH₃)}₂], 4.28 (overlap with *meso*-isomer) [m, 2H, CH₂{(CHSAc)(CO₂CH₃)}₂].

4.3.3. Rac- and meso-1,2-dithiolane-3,5-dicarboxylic acids—*Rac*- and *meso*-1,2-dithiolane-3,5-dicarboxylic acids have been previously reported [17], but an alternative route was used here. Dimethyl-2,4-bis(acetylthio)glutarate (3.05 g, 9.89 mmol) was added to a solution of KHCO₃ (10.0 g, 99.90 mmol) in H₂O (*ca.* 100 mL) and the biphasic mixture was refluxed for 6 hours in air, thereby resulting in the formation of a single yellow aqueous phase. The solution was allowed to cool to room temperature and then placed in an ice bath. HCl (1 M) was added to adjust the pH to a value of 1 (*caution: stench!*) and the solution was extracted into ethyl acetate. The extract was dried with MgSO₄ and then concentrated *in vacuo* to give a mixture of *rac*- and *meso*-1,2-dithiolane-3,5-dicarboxylic acids as a *ca.* 1:1 ratio, together with other impurities. The solution was placed at −15 °C, thereby depositing crystals of *rac*-1,2-dithiolane-3,5-dicarboxylic acid (270 mg, 14%). The mother liquor contained both *rac* and *meso* isomers, and repeated crystallizations deposited more *rac*-1,2-dithiolane-3,5-dicarboxylic acid, thereby enriching the mother liquor in *meso*-1,2-dithiolane-3,5-dicarboxylic acid. Although neither compound was obtained isomerically pure, the purity (*rac ca.* 95%, *meso ca.* 90%) was sufficient for the synthesis of the dithiol compounds, which could be purified *via* crystallization from Et₂O (*vide infra*). *Rac* isomer ¹H NMR (*d*₆-acetone): 2.74 [t, ³*J*_{H-H} = 6 Hz, 2H, CH₂{(CHS-)(CO₂H)}₂], 4.55 [t, ³*J*_{H-H} = 6 Hz, 2H, CH₂{(CHS-)(CO₂H)}₂]. *Meso* isomer ¹H NMR (*d*₆-acetone): 2.83 [t, ³*J*_{H-H} = 7 Hz, 2H, CH₂{(CHS-)(CO₂H)}₂], 4.44 [t, ³*J*_{H-H} = 7 Hz, 2H, CH₂{(CHS-)(CO₂H)}₂].

4.3.4. Rac-2,4-dimercaptoglutaric acid—*Rac*-2,4-dimercaptoglutaric acid has been previously reported [17], but an alternative route was used here. A suspension of *rac*-1,2-dithiolane-3,5-dicarboxylic acid (555 mg, 2.86 mmol) in water (*ca.* 10 mL) was treated with NaHCO₃ (264 mg, 3.14 mmol), thereby resulting in evolution of CO₂. Zn powder (1.00 g, 15.3 mmol) was added, and the mixture was stirred for 30 min. After this period, HCl(aq) (1.0 M, 32.0 mL, 32.0 mmol) was added and the mixture was filtered into a flask containing HCl(aq) (1.0 M, 8.0 mL, 8.0 mmol) to prevent regeneration of *rac*-1,2-dithiolane-3,5-dicarboxylic acid. The solution was extracted with ethyl acetate and the organic layer was dried with Na₂SO₄, after which the volatile components were removed *in vacuo* to give colorless *rac*-2,4-dimercaptoglutaric acid that was recrystallized from Et₂O (400 mg, 71%; literature yield 58% [17]). ¹H NMR *d*₆-acetone: 2.28 [t, ³*J*_{H-H} = 8 Hz, 2H, CH₂{(CHSH)(CO₂H)}₂], 3.60 [t, ³*J*_{H-H} = 8 Hz, 2H, CH₂{(CHSH)(CO₂H)}₂].

4.3.5. Meso-2,4-dimercaptoglutaric acid—*Meso*-2,4-dimercaptoglutaric acid has been previously reported [17], but an alternative route was used here. A suspension of *meso*-1,2-dithiolane-3,5-dicarboxylic acid (525 mg, 2.70 mmol, *ca.* 90% *meso*) in water (*ca.* 10 mL) was treated with NaHCO₃ (250 mg, 2.98 mmol), thereby resulting in evolution of CO₂. Zn powder (900 mg, 13.76 mmol) was added, and the mixture was stirred for 2 h. After this period, HCl(aq) (1.0 M, 32.0 mL, 32.0 mmol) was added and the mixture was filtered into a flask containing HCl(aq) (1.0 M, 8.0 mL, 8.0 mmol) to prevent regeneration of *meso*-1,2-dithiolane-3,5-dicarboxylic acid. The solution was extracted with Et₂O and the organic layer was dried with Na₂SO₄, after which the volatile components were removed *in vacuo* to give colorless crystals of *meso*-2,4-dimercaptoglutaric acid that were washed with cold Et₂O (150 mg, 28%; literature 8% [17]), together with a small amount of the *rac* isomer (*ca.* 5%). ¹H NMR (D₂O): 2.17 [m, 1H, CH₂{(CHSH)(CO₂H)}₂], 2.56 [m, 1H, CH₂{(CHSH)(CO₂H)}₂], 3.69 [t, ³J_{H-H} = 7 Hz, 2H, CH₂{(CHSH)(CO₂H)}₂].

4.3.6. Chelation studies—Male Wistar rats, weighing 150–175 g, were obtained from Harlan (Indianapolis, IN). Rats were injected intravenously as described previously [37]. Briefly, rats were anesthetized using isoflurane and a small incision was made to expose the femoral vein and artery. A non-toxic dose of HgCl₂ containing radioactive mercury ([²⁰³Hg]) in normal saline (0.5 μmol in 2 mL, i.e. 0.25 mM) was administered into the vein at a dose of 2 mL per kg body weight, corresponding to approximately 1 μCi per rat. [²⁰³Hg] was generated by irradiation of mercuric oxide at the University of Missouri Research Reactor (MURR) as described previously [41]. Twenty-four hours after injection with HgCl₂, rats were injected intraperitoneally with either saline or a dose of H₃DMPS, H₄DMSA, *rac*-H₄DMGA, or H₃DMCP (see Figs. 14–16). Animals were sacrificed 24 h later and blood and organs were harvested for estimation of mercury content. Urine and feces were collected after each 24 h period.

4.3.7. Data analyses—Data from animal experiments were analyzed with the Kolmogorov–Smirnov test for normality and Levene’s test for homogeneity of variances. Following these tests, data were analyzed using a one-way analysis of variance (ANOVA) to assess differences among the means. When statistically significant *F*-values were obtained with ANOVA, the data were analyzed using Tukey’s *post hoc* multiple comparison test. A *p*-value of <0.05 was considered statistically significant. Each group of animals contained three or four rats. All data are expressed as mean ± standard error.

Acknowledgments

Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Numbers R01GM046502 (G.P.) and ES019991 (C.C.B.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Appendix A. Supplementary data

CCDC 926429–926431 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/contents/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk.

References

- [1]. (a) Andersen P. Chem. Rev. 1999; 99:2683. [PubMed: 11749497] (b) Blanus M, Varnai VM, Piasek M, Kostial K. Curr. Med. Chem. 2005; 12:2771. [PubMed: 16305472]

- [2]. (a) Rooney JPK. *Toxicology*. 2007; 234:145. [PubMed: 17408840] (b) Guzzi G, La Porta CAM. *Toxicology*. 2008; 244:1. [PubMed: 18077077]
- [3]. (a) Aposhian HV, Maiorino RM, Gonzalez-Ramirez D, Zuniga-Charles M, Xu Z, Hurlbut KM, Junco-Munoz P, Dart RC, Aposhian MM. *Toxicology*. 1995; 97:23. [PubMed: 7716789] (b) Risher JF, Amler SN. *Neurotoxicology*. 2005; 26:691. [PubMed: 16009427] (c) Baum CR. *Curr. Opin. Pediatr.* 1999; 11:265. [PubMed: 10349108] (d) Aaseth J, Jacobsen D, Andersen O, Wickstrøm E. *Analyst*. 1995; 120:853. [PubMed: 7741240] (e) Domingo JL. *Reprod. Toxicol.* 1995; 9:105. [PubMed: 7795320] (f) Aposhian HV. *Annu. Rev. Pharmacol. Toxicol.* 1983; 23:193. [PubMed: 6307120] (g) Berlin, M.; Zalups, RK.; Fowler, BA. *Handbook on the Toxicology of Metals*. 3rd ed.. Elsevier Academic Press Inc; San Diego: 2007. Mercury; p. 675-729. Chapter 33
- [4]. (a) Clarkson TW, Magos L. *Crit. Rev. Toxicol.* 2006; 36:609. [PubMed: 16973445] (b) Mutter J, Naumann J, Guethlin C. *Crit. Rev. Toxicol.* 2007; 37:537. [PubMed: 17661216] (c) Clarkson TW. *Environ. Health Perspect. Suppl.* 2002; 110:11. (d) Alessio L, Campagna M, Lucchini R. *Am. J. Ind. Med.* 2007; 50:779. [PubMed: 17918211] (e) Clarkson TW, Vyas JB, Ballatori N. *Am. J. Ind. Med.* 2007; 50:757. [PubMed: 17477364] (f) Risher JF, De Rosa CT, Environ J. *Health*. 2007; 70:9. (g) Onyido I, Norris AR, Buncel E. *Chem. Rev.* 2004; 104:5911. [PubMed: 15584692]
- [5]. Zalups RK, Bridges CC. *Chem. Res. Toxicol.* 2012; 25:1825. [PubMed: 22667351]
- [6]. Correspondingly, there is also considerable effort directed towards environmental removal of mercury. See, for example: Hutchison AR, Atwood DA. *J. Chem. Crystallogr.* 2003; 33:631–645. Atwood DA, Zaman MK. *Struct. Bond.* 2006; 120:163–182. Blue LY, Van Aelstyn MA, Matlock M, Atwood DA. *Water Res.* 2008; 42:2025–2028. [PubMed: 18207488] Blue LY, Jana P, Atwood DA. *Fuel*. 2010; 89:1326–1330. Zaman KM, Blue LY, Huggins FE, Atwood DA. *Inorg. Chem.* 2007; 46:1975–1980. [PubMed: 17323915] Parham H, Zargar B, Shiralipour R. *J. Hazard. Mater.* 2012; 205:94–100. [PubMed: 22244341] Fu F, Wang Q. *J. Environ. Manage.* 2011; 92:407–418. [PubMed: 21138785]
- [7]. (a) George GN, Prince RC, Gailer J, Buttigieg GA, Denton MB, Harris HH, Pickering IJ. *Chem. Res. Toxicol.* 2004; 17:999. [PubMed: 15310232] (b) George GN, Pickering IJ, Doonan CJ, Korbas M, Singh SP, Hoffmeyer RE. *Adv. Mol. Toxicol.* 2008; 2:123.
- [8]. (a) Riedmaier AE, Nies AT, Schaeffeler E, Schwab M. *Pharmacol. Rev.* 2012; 64:421. [PubMed: 22457399] (b) Miyazaki H, Sekine T, Endou H. *Trends Pharmacol. Sci.* 2004; 25:654. [PubMed: 15530644] (c) Sekine T, Miyazaki H, Endou H. *Am. J. Physiol. Renal Physiol.* 2006; 290:F251. [PubMed: 16403838] (d) Zhou F, You G. *Pharm. Res.* 2007; 24:28. [PubMed: 17103332]
- [9]. Zalups, RK.; Bridges, CC. *Cellular and Molecular Biology of Metals*. Zalups, RK.; Koropatnick, J., editors. CRC Press; New York: 2010. Chapter 2
- [10]. (a) Silver A, Koch SA, Millar M. *Inorg. Chim. Acta.* 1993; 205:9. (b) Hoffmann GG, Steinfatt I, Brockner W, Kaiser V. *Z. Naturforsch. (B)*. 1999; 54:887. (c) Melnick JG, Yurkerwich K, Buccella D, Sattler W, Parkin G. *Inorg. Chem.* 2008; 47:6421. [PubMed: 18533648] (d) Sattler W, Yurkerwich K, Parkin G. *Dalton Trans.* 2009:4327. [PubMed: 19662310]
- [11]. (a) Christou G, Folting K, Huffman JC. *Polyhedron*. 1984; 3:1247. (b) Gruff ES, Koch SA. *J. Am. Chem. Soc.* 1990; 112:1245. (c) Santos RA, Gruff ES, Koch SA, Harbison GS. *J. Am. Chem. Soc.* 1991; 113:469. (d) Watton SP, Wright JG, MacDonnell FM, Bryson JW, Sabat M, O'Halloran TV. *J. Am. Chem. Soc.* 1990; 112:2824. (e) Alsina T, Clegg W, Fraser KA, Sola J. *J. Chem. Soc., Dalton Trans.* 1992:1393. (f) Alcock NW, Lampe PA, Moore P. *J. Chem. Soc., Dalton Trans.* 1980:1471.
- [12]. (a) Manceau A, Nagy KL. *Dalton Trans.* 2008; 1421. (b) Wright JG, Natan MJ, MacDonnell FM, Ralston DM, O'Halloran TV. *Prog. Inorg. Chem.* 1990; 38:323. (c) Holloway CE, Melnik M. *Main Group Metal Chem.* 1994; 17:799.
- [13]. (a) Wilhelm M, Deeken S, Berssen E, Saak W, Lützen A, Koch R, Strasdeit H. *Eur. J. Inorg. Chem.* 2004:2301. (b) Blake AJ, Pasteur EC, Reid G, Schröder M. *Polyhedron*. 1991; 10:1545. (c) Setzer WN, Tang YP, Grant GJ, VanDerveer DG. *Inorg. Chem.* 1991; 30:3652. (d) Pickardt J, von Chrzanowski L, Steudel R, Borowski M. *Z. Naturforsch. (B)*. 2004; 59:1077. (e) Blower PJ, Chadwick AV, Jeffery JC, Mullen GED, Powell AK, Salek SN, Smith RJ, Went MJ. *Inorg. Chim. Acta.* 1999; 294:170. (f) Alcock NW, Herron N, Moore P. *J. Chem. Soc., Dalton Trans.*

1978:394.(g) Grant GJ, Botros ME, Hassler JS, Janzen DE, Grapperhaus CA, O'Toole MG, VanDerveer DG. *Polyhedron*. 2008; 27:3097.(h) Helm ML, Combs CM, VanDerveer DG, Grant GJ. *Inorg. Chim. Acta*. 2002; 338:182.(i) Knorr M, Peindy HN, Guyon F, Sachdev H, Strohmann C. *Z. Anorg. Allg. Chem.* 2004; 630:1955.(j) Sakakibara M, Yonemura Y, Tanaka Z, Matsumoto S, Fukuyama K, Matsuura H, Murata H. *J. Mol. Struct.* 1980; 69:53.

- [14]. (a) Bigoli F, Cabras MC, Deplano P, Mercuri ML, Marchiò L, Serpe A, Trogu EF. *Eur. J. Inorg. Chem.* 2004:960.(b) Cannas M, Devillanova FA, Marongiu G, Verani G. *J. Inorg. Nucl. Chem.* 1981; 43:2383.(c) Norris AR, Taylor SE, Buncel E, Belangergariepy F, Beauchamp AL. *Can. J. Chem.* 1983; 61:1536.(d) Cheung KK, McEwen RS, Sim GA. *Nature*. 1965; 205:383.(e) Brotherton PD, Healy PC, Raston CL, White AH. *J. Chem. Soc., Dalton Trans.* 1973:334.(f) White JL, Tanski JM, Churchill DG, Rheingold AL, Rabinovich D. *J. Chem. Crystallogr.* 2003; 33:437.(g) Melnick JG, Yurkerwich K, Parkin G. *Inorg. Chem.* 2009; 48:6763. [PubMed: 20507113]
- [15]. (a) Parkin G. *New J. Chem.* 2007; 31:1996.(b) Rabinovich D. *Struct. Bond.* 2006; 120:143.(c) Melnick JG, Parkin G. *Science*. 2007; 317:225. [PubMed: 17626880] (d) Melnick JG, Yurkerwich K, Parkin G. *J. Am. Chem. Soc.* 2010; 132:647. [PubMed: 20020759] (e) White JL, Tanski JM, Rabinovich D. *Dalton Trans.* 2002; 15:2987.(f) Cassidy I, Garner M, Kennedy AR, Potts GBS, Reglinski J, Slavin PA, Spicer MD. *Eur. J. Inorg. Chem.* 2002; 5:1235.(g) Bailey PJ, Dawson A, McCormick C, Moggach SA, Oswald IDH, Parsons S, Rankin DWH. *Inorg. Chem.* 2005; 44:8884. [PubMed: 16296844] (h) Alvarez HM, Tran TB, Richter MA, Alyounes DM, Rabinovich D, Tanski JM, Krawiec M. *Inorg. Chem.* 2003; 42:2149. [PubMed: 12639154] (i) Cetin A, Ziegler CJ. *Dalton Trans.* 2006; 8:1006. [PubMed: 16474885]
- [16]. (a) Canty AJ, Kishimoto R. *Nature*. 1975; 255:123. [PubMed: 1110756] (b) Canty AJ, Kishimoto R. *Inorg. Chim. Acta*. 1977; 24:109.(c) Arnold AP, Canty AJ, Moors PW, Deacon GB. *J. Inorg. Biochem.* 1983; 19:319. [PubMed: 6655472] (d) Arnold AP, Canty AJ, Reid RS, Rabenstein DL. *Can. J. Chem.* 1985; 63:2430.(e) Wille K, Moran JK, Roundhill DM. *Polyhedron*. 1990; 9:597.(f) Fang X, Hua F, Fernando Q. *Chem. Res. Toxicol.* 1996; 9:284. [PubMed: 8924605]
- [17]. (a) Hedblom M-O. *J. Agric. Res.* 1971; 1:43.(b) Hedblom M-O. *Tetrahedron Lett.* 1970:5159.
- [18]. Pyrka GJ, Scott N, Fernando Q. *Acta Crystallogr.* 1992; C48:2007.
- [19]. Fang X, Fernando Q. *Chem. Res. Toxicol.* 1994; 7:148. [PubMed: 8199302]
- [20]. The ability of DMF to preferentially hydrogen bond to carboxylic acid moieties and thereby reduce the dimensionality of other polycarboxylic acid derivatives has also been noted. See, for example: Dale SH, Elsegood MRJ. *Acta Crystallogr.* 2004; C60:o444–o448. Xu XL, Kennedy AR, Florence AJ, Shankland N. *Acta Crystallogr.* 2004; E60:o1950–o1951.
- [21]. Cambridge Structural Database (Version 5.33), 3D search and research using the Cambridge Structural Database, in: Allen FH, Kennard O. *Chemical Design Automation News*. 1993; 8(1):1, 31–37.
- [22]. Allen FH, Bird CM, Rowland RS, Raithby PR. *Acta Crystallogr.* 1997; B53:696.
- [23]. (a) Singh R, Whitesides GM. *J. Am. Chem. Soc.* 1990; 112:1190.(b) Yanagawa H, Kato T, Sagami H, Kitahara Y. *Synthesis*. 1973:607.(c) Schotte L, Ström H. *Acta Chem. Scand.* 1956; 10:687.
- [24]. (a) Cikrt M, Tichy M, Jones MM. *Res. Commun. Chem. Path. Pharmacol.* 1982; 38:421.(b) Kuschinsky G, Muscholl E. *Arch. Exp. Path. Pharmacol.* 1954; 223:408.
- [25]. Fu J, Hoffmeyer RE, Pushie MJ, Singh SP, Pickering IJ, George GN. *J. Biol. Inorg. Chem.* 2011; 16:15. [PubMed: 20740295]
- [26]. It should be noted that although chelated structures have been postulated for coordination of $[\text{H}_2\text{DMSA}]^{2-}$ to heavy metals (Ref. [3a, 26a–d]), none of these species has been structurally characterized by X-ray diffraction (see, for example Ref. [7]). Rivera M, Zheng W, Aposhian HV, Fernando Q. *Toxicol. Appl. Pharmacol.* 1989; 100:96–106. [PubMed: 2548305] Rivera M, Aposhian HV, Fernando Q. *J. Inorg. Biochem.* 1989; 37:283–293. [PubMed: 2560792] Bradberry S, Vale A. *Clin. Toxicol.* 2009; 47:617–631. Fang X, Fernando Q. *Chem. Res. Toxicol.* 1995; 8:525–536. [PubMed: 7548732]
- [27]. Taylor NJ, Carty AJ. *J. Am. Chem. Soc.* 1977; 99:6143. [PubMed: 893885]
- [28]. For other three-coordinate mercury compounds that feature sulfur ligands, see: Vittal JJ, Dean PAW. *Inorg. Chem.* 1996; 35:3089–3093. [PubMed: 11666502] Bochmann M, Webb KJ, Powell

- AK. *Polyhedron*. 1992; 11:513–516. Singh G, Singh AK, Drake JE, Hursthouse MB, Light ME. *Polyhedron*. 2006; 25:2915–2919. Nam HJ, Lee H-J, Noh D-Y. *Polyhedron*. 2004; 23:115–123.
- [29]. (a) Wright JG, Tsang H-T, Penner-Hahn JE, O'Halloran TV. *J. Am. Chem. Soc.* 1990; 112:2434. (b) Fleissner G, Reigle MD, O'Halloran TV, Spiro TG. *J. Am. Chem. Soc.* 1998; 120:12690. (c) Utschig LM, Bryson JW, O'Halloran TV. *Science*. 1995; 268:380. [PubMed: 7716541] (d) Huffman DL, Utschig LM, O'Halloran TV. *Metal Ions Biol. Syst.* 1997; 34:503.
- [30]. (a) Ali BF. *J. Chem. Crystallogr.* 2005; 35:589. (b) Yan C-F, Yue C-Y, Wu M-Y, Chen L, Feng R, Jiang F-L, Hong M-C. *Chin. J. Struct. Chem.* 2009; 28:453. (c) Tang X-Y, Chen J-X, Liu G-F, Ren Z-G, Zhang Y, Lang J-P. *Eur. J. Inorg. Chem.* 2008:2593.
- [31]. More complex structures also exist in mercury thiolate halide systems. See, for example: Bharara MS, Parkin S, Atwood DA. *Inorg. Chem.* 2006; 45:7261–7268. [PubMed: 16933927] Bharara MS, Parkin S, Atwood DA. *Inorg. Chem.* 2006; 45:2112–2118. [PubMed: 16499374] Bharara MS, Bui TH, Parkin S, Atwood DA. *Inorg. Chem.* 2005; 44:5753–5760. [PubMed: 16060627] Bharara MS, Bui TH, Parkin S, Atwood DA. *Dalton Trans.* 2005:3874–3880. [PubMed: 16311641]
- [32]. For examples of three-coordinate “Y”-shaped mercury compounds with S–Hg–S angles close to 90°, see: Noh D-Y, Underhill AE, Hursthouse MB. *Chem. Commun.* 1997:2211–2212. Baba K, Okamura TA, Yamamoto H, Yamamoto T, Ueyama N. *Inorg. Chem.* 2008; 47:2837–2848. [PubMed: 18330987] Kim Y-Y, Lee H-J, Nam HJ, Noh D-Y. *Bull. Korean Chem. Soc.* 2001; 22:17–18.
- [33]. Even more acute S–Hg–S angles are observed for ligands in which the sulfur atoms are separated by a single atom, but in such cases the Hg–S bond lengths are no longer similar. See, for example: Singh V, Chauhan R, Kumar A, Bahadur L, Singh N. *Dalton Trans.* 2010; 39:9779–9788. [PubMed: 20830401] Singh N, Kumar A, Molloy KC, Mahon MF. *Dalton Trans.* 2008:4999–5007. [PubMed: 18802612]
- [34]. For examples of three-coordinate mercury compounds with S–Hg–S angles close to 180°, see: Kato M, Kojima K, Kamura TA, Yamamoto H, Yamamura T, Ueyama N. *Inorg. Chem.* 2005; 44:4037–4044. [PubMed: 15907133] Chen JX, Zhang WH, Tang XY, Ren ZG, Zhang Y, Lang JP. *Inorg. Chem.* 2006; 45:2568–2580. [PubMed: 16529478]
- [35]. For other examples of mercury compounds that contain a 5-membered –S–Hg–S– chelate ring, see Refs. [11f,14a,32c] and Glick MD, Ilsley WH, Siedle AR. *Inorg. Chem.* 1981; 20:3819–3822. Singh G, Bali S, Singh AK, Drake JE, Macdonald CLB, Hursthouse MB, Little ME. *Inorg. Chim. Acta*. 2005; 358:912–918. Baggio R, Garland MT, Percec M. *J. Chem. Soc., Dalton Trans.* 1995:987–992. Baudron SA, Hosseini MW. *Inorg. Chem.* 2006; 45:5260–5262. [PubMed: 16813382] LeNarvor N, Robertson N, Wallace E, Kilburn JD, Underhill AE, Bartlett PN, Webster M. *J. Chem. Soc., Dalton Trans.* 1996:823–828.
- [36]. For examples of mercury compounds that contain a 6-membered –S–Hg–S– chelate ring, see Ref. [13i] and: Aragoni MC, Arca M, Carrea MB, Demartin F, Devillanova FA, Garau A, Isaia F, Lippolis V, Verani G. *Eur. J. Inorg. Chem.* 2004:4660–4668. Lobana TS, Singh R, Sandhu MK, Tiekink ERT. *J. Coord. Chem.* 1991; 24:29–33. Bumbu O, Varga AR, Silvestru A. *Rev. Roum. Chim.* 2004; 49:269–278. Peindy HN, Guyon F, Knorr M, Smith AB, Farouq JA, Islas SA, Rabinovich D, Golen JA, Strohmman C. *Inorg. Chem. Commun.* 2005; 8:479–482.
- [37]. Bridges CC, Joshee L, Zalups RK. *J. Pharmacol. Exp. Ther.* 2008; 324:383. [PubMed: 17940195]
- [38]. Gottlieb HE, Kotlyar V, Nudelman A. *J. Org. Chem.* 1997; 62:7512. [PubMed: 11671879]
- [39]. Ingold CK. *J. Chem. Soc. Trans.* 1921; 119:305–329.
- [40]. (a) Sheldrick, GM. *SHELXTL*, an Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data. University of Göttingen; Göttingen, Federal Republic of Germany: 1981. (b) Sheldrick GM. *Acta Crystallogr.* 2008; 64:112. Sect. A.
- [41]. Bridges CC, Bauch C, Verrey F, Zalups RK. *J. Am. Soc. Nephrol.* 2004; 15:663. [PubMed: 14978168]

Fig. 1.
Chelating agents that have been employed in mercury detoxification.

Fig. 2.
1,3-Dithiols that contain carboxylic acid moieties.

Fig. 3.
Molecular structure of *meso*-H₄DMGA.

Fig. 4.
Molecular structure of *rac*-H₄DMGA.

Fig. 5.
A portion of the polymeric hydrogen bonded structure of *meso*-H₄DMGA. Hydrogen bonding interactions are represented with hollow bonds.

Fig. 6.

A portion of the polymeric hydrogen bonded structure of *rac*-H₄DMGA. Hydrogen bonding interactions are represented with hollow bonds.

Fig. 7. Hydrogen bonded sheet-like structure of *rac*-H₄DMSA (coordinates taken from Ref. [19]). Hydrogen bonding interactions are represented with hollow bonds.

Fig. 8.

Hydrogen bonding in the 1:2 adduct of *meso*-H₄DMSA and DMF. O–H...O hydrogen bonds link together the *meso*-H₄DMSA and DMF, while longer S–H...O interactions create an extended array (coordinates taken from Ref. [18]). Hydrogen bonding interactions are represented with hollow bonds.

Fig. 9.
Molecular structure of 2-carboxy-1,3-propanedithiol (hydrogen bonded dimer shown).
Hydrogen bonding interactions are represented with hollow bonds.

Fig. 10.

Views of the S-C-C-S torsion angles of *meso*-H₄DMGA, *rac*-H₄DMGA and H₃DMCP.

Fig. 11.

Geometry optimized structures of LHg (L = *meso*-H₂DMGA²⁻, *rac*-H₂DMGA²⁻, HDMCP²⁻, *meso*-H₂DMSA²⁻ and *rac*-H₂DMSA²⁻).

Fig. 12. Geometry optimized structures of L Hg^{Q} ($\text{L} = \text{meso-DMGA}^{4-}$, rac-DMGA^{4-} , DMCP^{3-} , meso-DMSA^{4-} and rac-DMSA^{4-}).

Fig. 13.

Geometry optimized structures of $[\text{LHgCl}]^Q$ ($\text{L} = \text{meso-H}_2\text{DMGA}^{2-}$, $\text{rac-H}_2\text{DMGA}^{2-}$, HDMCP^{2-} , $\text{meso-H}_2\text{DMSA}^{2-}$ and $\text{rac-H}_2\text{DMSA}^{2-}$).

Fig. 14.

Renal burden of mercury in rats exposed to HgCl_2 ($0.5 \mu\text{mol}$ per kg body weight, delivered as a 0.25 mM solution) and treated subsequently with saline (2 mL per kg) or chelator (50 mg per kg body weight, delivered as a 25 mg mL^{-1} solution). An asterisk (*) indicates a value that is significantly different from the mean value for saline-injected rats ($p < 0.05$).

Fig. 15. Hepatic (A) and hematologic (B) burden of mercury in rats exposed to HgCl₂ (0.5 μmol per kg body weight, delivered as a 0.25 mM solution) and treated subsequently with saline (2 mL per kg) or chelator (50 mg per kg body weight, delivered as a 25 mg mL⁻¹ solution). An asterisk (*) indicates a value that is significantly different from the mean value for saline-injected rats (*p* < 0.05).

Fig. 16. Amount of mercury in urine (A) and feces (B) of rats exposed to HgCl_2 (0.5 μmol per kg body weight, delivered as a 0.25 mM solution) and treated subsequently with saline (2 mL per kg body weight) or chelator (50 mg per kg body weight, delivered as a 25 mg mL^{-1} solution). An asterisk (*) indicates a value that is significantly different from the mean value for saline-injected rats ($p < 0.05$).

Scheme 1.
Synthesis of *rac*(±)- and *meso*-2,4-dimercaptoglutaric acid.

Table 1

Torsion angles and S...S distances for selected dithiol compounds

Compound	S–C C–S torsion angle (°)	S S distance (Å)	Refs.
<i>meso</i> -H ₄ DMGA	119.6	4.94	this work
<i>rac</i> -H ₄ DMGA	116.2	4.30	this work
H ₃ DMCP	126.0	4.97	this work
<i>meso</i> -H ₄ DMSA(DMF) ₂	180.0	4.44	[18]
<i>rac</i> -H ₄ DMSA	66.2	3.44	[19]

Table 2

Selected bond lengths and angles for geometry optimized structures of LHg (L = *meso*-H₂DMGA²⁻, *rac*-H₂DMGA²⁻, HDMCP²⁻, *meso*-H₂DMSA²⁻ and *rac*-H₂DMSA²⁻)

Compound	$d(\text{Hg}-\text{S}_1)$ (Å)	$d(\text{Hg}-\text{S}_2)$ (Å)	$d(\text{Hg}-\text{O})^a$ (Å)	$\text{S}_1-\text{Hg}-\text{S}_2$ (°)
Hg(<i>meso</i> -H ₂ DMGA)	2.521	2.524	4.519	117.2
Hg(<i>rac</i> -H ₂ DMGA)	2.512	2.526	2.882	119.4
Hg(HDMCP)	2.510	2.511	2.788	123.1
Hg(<i>meso</i> -H ₂ DMSA)	2.556	2.580	2.764	96.2
Hg(<i>rac</i> -H ₂ DMSA)	2.544	2.544	5.209	97.4

^aShortest Hg–O distance.

Table 3

Selected bond lengths and angles for geometry optimized structures of L'HgQ (L' = *meso*-DMGA⁴⁻, *rac*-DMGA⁴⁻, DMCP³⁻, *meso*-DMSA⁴⁻ and *rac*-DMSA⁴⁻)

Compound	d(Hg-S ₁)(Å)	d(Hg-S ₂)(Å)	d(Hg-O) ^a (Å)	S ₁ -Hg-S ₂ (°)
[Hg(<i>meso</i> -DMGA)] ²⁻	2.544	2.616	2.413	109.2
[Hg(<i>rac</i> -DMGA)] ²⁻	2.532	2.590	2.434	112.8
[Hg(DMCP)] ⁻	2.551	2.551	2.360	114.3
[Hg(<i>meso</i> -DMSA)] ²⁻	2.600	2.658	2.434	96.8
[Hg(<i>rac</i> -DMSA)] ²⁻	2.600	2.639	2.444	90.5

^a Shortest Hg-O distance.

Table 4

Selected bond lengths and angles for geometry optimized structures of [LHgCl]Q (L = *meso*-H₂DMGA²⁻, *rac*-H₂DMGA²⁻, HDMCP²⁻, *meso*-H₂DMSA²⁻ and *rac*-H₂DMSA²⁻)

Compound	d(Hg-S ₁)(Å)	d(Hg-S ₂)(Å)	d(Hg-Cl)(Å)	S ₁ -Hg-S ₂ (°)	S ₁ -Hg-Cl(°)	S ₂ -Hg-Cl(°)
[Hg(<i>meso</i> -H ₂ DMGA)Cl] ⁻	2.635	2.640	2.548	96.3	132.3	131.4
[Hg(<i>rac</i> -H ₂ DMGA)Cl] ⁻	2.629	2.638	2.543	95.8	132.8	131.3
[Hg(HDMCP)Cl] ⁻	2.592	2.630	2.561	105.0	131.6	123.4
[Hg(<i>meso</i> -H ₂ DMSA)Cl] ⁻	2.608	2.617	2.539	90.6	134.3	135.1
[Hg(<i>rac</i> -H ₂ DMSA)Cl] ⁻	2.599	2.639	2.529	89.3	139.5	131.1

Table 5

Crystal, intensity collection and refinement data

	<i>meso</i> -H ₄ DMGA	<i>rac</i> -H ₄ DMGA	H ₃ DMCP
Lattice	triclinic	monoclinic	monoclinic
Formula	C ₅ H ₈ O ₄ S ₂	C ₅ H ₈ O ₄ S ₂	C ₅ H ₈ O ₄ S ₂
Formula weight	196.23	196.23	152.22
Space group	<i>P</i> 1	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>n</i>
<i>Unit cell dimensions</i>			
<i>a</i> (Å)	6.8623(5)	6.8561(8)	9.719(5)
<i>b</i> (Å)	7.8506(5)	12.4153(15)	6.930(3)
<i>c</i> (Å)	8.5151(10)	10.0971(12)	10.475(5)
(°)	97.5080(10)	90	90
(°)	91.8010(10)	106.796(2)	110.663(7)
(°)	114.5930(10)	90	90
<i>V</i> (Å ³)	411.67(6)	822.81(17)	660.1(6)
<i>Z</i>	2	4	4
<i>T</i> (K)	125(2)	125(2)	125(2)
(Å)	0.71073	0.71073	0.71073
(g cm ⁻³)	1.583	1.584	1.532
μ (Mo K α) (mm ⁻¹)	0.610	0.611	0.715
max (°)	30	32.43	32.25
No. of data collected	7168	13928	8634
No. of data	2807	2867	2258
No. of parameters	110	110	85
<i>R</i> _{<i>I</i>} [I>2 (<i>I</i>)]	0.0400	0.0482	0.0457
<i>wR</i> ₂ [I>2 (<i>I</i>)]	0.1031	0.1343	0.1085
<i>R</i> _{<i>I</i>} [all data]	0.0510	0.0687	0.0845
<i>wR</i> ₂ [all data]	0.1102	0.1491	0.1305
Goodness-of-fit (GOF) on <i>I</i> ²	1.039	1.058	1.023