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Addressing Lead Toxicity: Complexation of Lead(II) with Thiopyrone and Hydroxypyridinethione O,S Mixed Chelators

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The lead(II) ion is regarded as a serious environmental contaminant. A considerable need exists to develop selective ligands for remediation of this metal ion. Herein, the coordination chemistry of lead(II) is investigated with three O,S donor ligands: thiomaltol, 3-hydroxy-1-methyl-2(1*H*)-pyridinethione (3,2-HOPTO), and 3-hydroxy-1,2-dimethyl-4(1*H*)-pyridinethione (3,4-HOPTO). The X-ray structures of [Pb(thiomaltolato)$_2$] and [Pb(3,4-HOPTO)$_2$] have been solved, revealing the expected 4-coordinate geometries. Electronic spectra have been obtained for the lead(II) complexes with all three ligands. Preliminary solution studies show that the thiomaltol ligand binds lead(II) preferentially over magnesium(II) and calcium(II); however, [Pb(thiomaltolato)$_2$] is not stable in the presence of 1 equiv of EDTA. Tetradentate ligands derived from these O,S chelators are expected to generate higher affinity ligands for lead(II) sequestration.

The coordination chemistry of the lead(II) ion has remained a subject of continuing interest due to the persistence of this metal ion as a high priority environmental toxin,[1−3] and substantial effort has been invested in the design of selective sensors of lead to detect this pollutant.[4−7] Significant advancements, by using both biochemical and model-based studies,[8] have been made in understanding the molecular mechanisms that cause lead toxicity.[9] The ability of lead(II) to undergo metathesis reactions with zinc(II) and calcium(II) metalloproteins resulting in loss of metabolic function continues to be a primary hypothesis underlying the detrimental effects of lead exposure.[10,11]

In light of the continued interest in understanding lead toxicity and detecting this widespread contaminant, progress toward designing and characterizing lead-selective ligands remains an important topic.[1,12] Compounds presently used for lead chelation therapy, such as 2,3-dimercaptopropanol (British Anti-Lewisite, BAL) and *meso*-2,3-dimercaptosuccinic acid (DMSA), were not specifically optimized for "heavy" metal chelation and suffer from side effects associated with this lack of selectivity. The identification of high affinity ligands for lead would prove useful not only for treating lead poisoning, but also for developing molecular probes for elucidating the biodistribution and biological interactions of this ion in living systems. The work of Raymond and co-workers on thiohydroxamic acids has often been cited as a noteworthy effort toward the development of lead(II) specific sequestering agents (Figure 1).[13−16] These mixed O,S donor ligands are proposed to have an optimal hard/soft Lewis basicity to match the preferences of the lead(II) ion and as such have been reported to form extremely stable lead(II) complexes (log $\beta_{120} = 20.7$, for *N*-phenylthiobenzohydroxamic acid in 70% aqueous dioxane).[17] Despite these encouraging results, no significant advancements of these systems have been reported for nearly a decade. Herein, we report several O,S ligands, including thiopyrones and hydroxypyridinethiones, which form stable, mononuclear complexes with lead(II) and may be promising new selective chelators for this biologically toxic metal ion.

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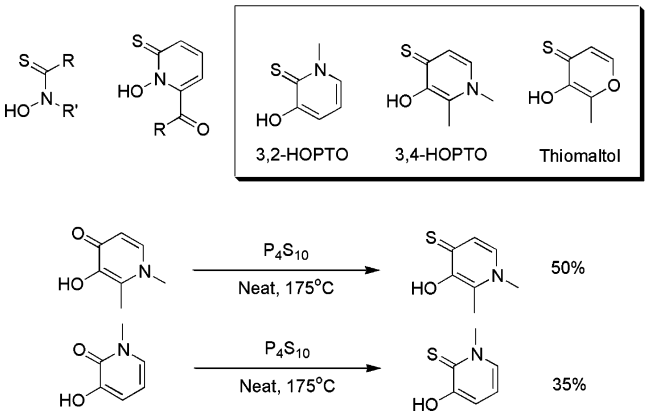

Figure 1. Mixed O,S ligands studied for selective lead(II) complexation. Thiohydroxamic acids and 1,2-HOPTO ligands (top, outside box) had been previously synthesized and studied for lead(II) sequestration. New ligands 3,2-HOPTO, 3,4-HOPTO, and thiomaltol (left to right, in box) are presented here. One-step synthesis of 3,4-HOPTO and 3,2-HOPTO (bottom).

An efficient synthesis of thiopyrones derived from 3-hydroxy-2-methyl-4-pyrone (maltol) and 3-hydroxy-4-pyrone (pyromeconic acid) has been recently reported.[18] On the basis of these findings, we sought to prepare hydroxypyridinethiones (HOPTOs) derived from 3-hydroxy-1-methyl-2(1*H*)-pyridinone and 3-hydroxy-1,2-dimethyl-4(1*H*)-pyridinone. However, combination of these starting materials with P_4S_{10} with or without HMDO under a variety of solution conditions failed to generate the desired compounds.[18−20] Ultimately, a solventless reaction where the hydroxypyridinone starting material was pulverized with P_4S_{10} and heated to 175 °C under a nitrogen atmosphere allowed for isolation of the desired 3,2-HOPTO and 3,4-HOPTO products, respectively (Figure 1).[21] Reaction of thiomaltol or HOPTO ligands with lead(II) acetate proceeded smoothly in mixed aqueous/methanolic solution resulting in the precipitation of the lead complexes as yellow powders. A recent study reports the preparation of [V═O(3,4-HOPTO)$_2$] and its use as an insulin mimetic, but experimental details on the synthesis of 3,4-HOPTO or the vanadyl complex were not provided.[22]

Standard characterization of the lead(II) complexes with thiomaltol, 3,2-HOPTO, and 3,4-HOPTO was consistent with each of these ligands forming a 1:2 metal/ligand complex (see Supporting Information). The composition of these compounds was unambiguously confirmed by structural characterization of [Pb(thiomaltolato)$_2$] and [Pb(3,4-HOPTO)$_2$] by using single crystal X-ray diffraction.[23] The structures of these complexes are shown in Figure 2. Both complexes show a four-coordinate geometry around the lead(II) ion, quite similar to that observed in other O,S chelating complexes.[13−15] The bond lengths in each complex are similar, with Pb−S and Pb−O distances of 2.81 and 2.36 Å

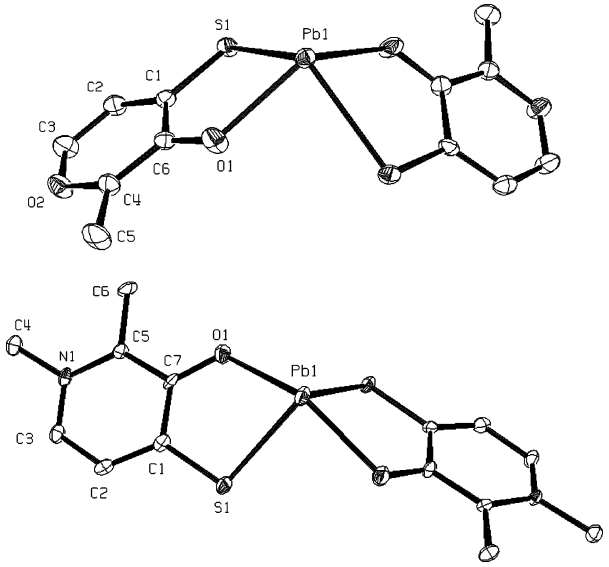

Figure 2. Structural diagram of [Pb(thiomaltolato)$_2$] (top) and [Pb(3,4-HOPTO)$_2$] (bottom) with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms have been omitted for clarity.

in [Pb(thiomaltolato)$_2$] and 2.67 and 2.39 Å in [Pb(3,4-HOPTO)$_2$]. These bond distances are comparable to those found in earlier thiohydroxamic acid complexes.[13−15] The coordination geometry around the lead(II) ion is distorted due to the stereoactive lone pair of the metal center. This irregular coordination geometry has been found in related compounds.[13−15] The crystal structures provide no evidence for bridging interactions between neighboring complexes, as has often been found in lead(II) complexes with thiohydroxamic acids and hydroxypyridinethiones (typically distant Pb···O interactions). The closest contact between neighboring complexes in both structures is a Pb···S contact of 3.50 and 4.37 Å for [Pb(thiomaltolato)$_2$] and [Pb(3,4-HOPTO)$_2$], respectively (Figures S1−S3). In the structure of [Pb(thiomaltolato)$_2$], the 3.50 Å contact is potentially within a weak bonding distance, but it appears to be more a result of the "nested" packing of the complexes than a specific interaction.

The electronic spectra of these complexes show several intense transitions. In DMF solution, [Pb(thiomaltolato)$_2$] shows two broad bands centered at 306 and 402 nm, while both [Pb(3,2-HOPTO)$_2$] and [Pb(3,4-HOPTO)$_2$] show a single broad transition at 376 and 378 nm, respectively but lack a well-defined, higher energy feature at ∼300 nm (Figure 3). The major transitions in all of the metal complexes are shifted to lower energy relative to the corresponding free ligands.[10]

The intense electronic transitions of these complexes provided a spectroscopic handle for a preliminary evaluation

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(23) X-ray data follow. Crystal data for [Pb(thiomaltolato)$_2$] ($PbC_{12}H_{10}O_4S_2$, M_r = 489.51 g mol^{-1}): monoclinic, space group *C*2/*c*, a = 19.397(14) Å, b = 4.131(3) Å, c = 16.584(12) Å, β = 91.865(10)°, V = 1328.2(16) Å^3, Z = 4, T = 100(2) K, wR_2 = 0.0827, R_1 = 0.0338 (1509 unique reflections). Crystal data for [Pb(3,4-HOPTO)$_2$] ($PbC_{14}H_{16}N_2O_2S_2$, M_r = 515.60 g mol^{-1}): orthorhombic, space group *Fdd*2, a = 8.7501(6) Å, b = 31.678(2) Å, c = 10.7750(7) Å, V = 2986.7(4) Å^3, Z = 4, T = 100(2) K, wR_2 = 0.0673, R_1 = 0.0261 (1694 unique reflections).

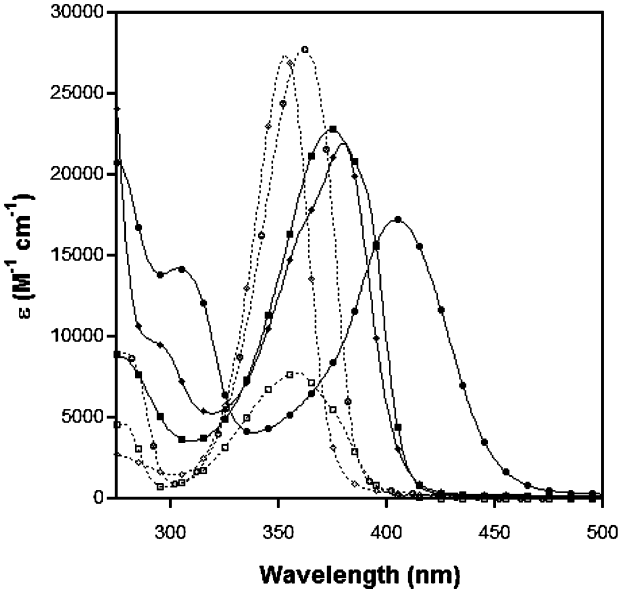

Figure 3. Electronic spectra of 3,2-HOPTO (□), 3,4-HOPTO (◇), and thiomaltol (○) ligands in DMF. Electronic spectra of [Pb(3,2-HOPTO)$_2$] (■), [Pb(3,4-HOPTO)$_2$] (◆), and [Pb(thiomaltolato)$_2$] (●) complexes in DMF. The complete spectra of the ligands are shown as dotted lines (···), and lead(II) complexes are shown as solid lines (—).

of the stability of these metal complexes in the presence of biologically relevant metal ions. [Pb(thiomaltolato)$_2$] was dissolved in an aqueous solution containing 1.0 M DMF (~12:1 v/v water/DMF) to a concentration of ~50 μM and titrated with increasing amounts of $CaCl_2$ or $MgCl_2$. The spectrum of the [Pb(thiomaltolato)$_2$] complex is essentially unchanged in the presence of ~50-fold excess of Mg^{2+} or Ca^{2+}, indicating the thiopyrone has some selectivity for lead(II) (Figure S4). The [Pb(thiomaltolato)$_2$] complex was also examined in the presence of EDTA in aqueous buffer. Incubation with 0.1 equiv of EDTA caused only small changes in the [Pb(thiomaltolato)$_2$] spectra; however, competition with either 1 or 10 equiv of EDTA showed a complete loss of the [Pb(thiomaltolato)$_2$] complex within ~24 h (Figure S5). This suggests that the stability of [Pb(thiomaltolato)$_2$] is significantly lower that that of the [Pb(EDTA)]$^{2-}$ complex (log β_{110} = 18.10).[1] Although we have not yet determined the formation constants for these complexes, the results are generally consistent with that found for simple thiohydroxamic acids. The stability constant of [Pb(acetothiohydroxamato)$_2$] is log β_{120} = 12.40 (in 1:1 MeOH/water), which is also substantially lower than that found for EDTA.[16] Tethering of two O,S chelators together to prepare a tetradentate ligand may improve the stability of the complexes reported here.

In summary, we have described a one-step synthesis for two hydroxypyridinethiones for which essentially no coordination chemistry has been described[22] and reported novel lead(II) complexes formed with O,S ligands. Spectrophotometric studies suggest that these O,S chelators have some selectivity for lead(II) over other biological relevant cations such as magnesium(II) and calcium(II). Ongoing studies are focused on a more detailed examination of the solution thermodynamics of these ligands with various metal ions as well as the synthesis of bis(bidentate) ligands with potentially greater affinity and selectivity for the toxic lead(II) ion.

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Supporting Information Available: Synthetic details for all new ligands and metal complexes, Table S1, Figures S1−S5. X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org. CIF data are also available free of charge via the Internet at http://www.ccdc.cam.ac.uk. Refer to CCDC reference numbers 235985 and 235986.

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