

Metal Complexes of the *trans*-Influencing Ligand Thiomaltol

Jana A. Lewis, David T. Puerta, and Seth M. Cohen*

Department of Chemistry and Biochemistry, University of California,
San Diego, La Jolla, California 92093-0358

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The wide use of the ligand 3-hydroxy-2-methyl-4-pyrone (maltol) in bioinorganic chemistry has prompted an effort to further exploit this ligand class by achieving an efficient, one-step synthesis of the chelator 3-hydroxy-2-methyl-4-thiopyrone (thiomaltol). Complexes of thiomaltol with nickel(II) and iron(III) have been prepared and studied by using UV–visible spectroscopy and electrochemical methods. In addition, both complexes as well as the free thiomaltol ligand have been structurally characterized by using single-crystal X-ray diffraction methods. The ligand is found to exert a strong *trans* influence on the structure of the complexes in the solid state with the nickel(II) and iron(III) complexes demonstrating a *cis* and *fac* geometry, respectively. The compounds described here should significantly expand the scope and utility of O,S-donor ligands derived from maltol and related precursors.

Introduction

3-Hydroxy-2-methyl-4-pyrone (maltol) is a natural product and a common food additive,¹ which has also been extensively used as a monoanionic, bidentate metal chelator. Metal complexes of maltol with a wide variety of transition and group 13/14 metals have been of significant interest, particularly in the bioinorganic community.^{2–6} Neutral, water-soluble complexes of maltol with aluminum(III) have been used to examine the role that this metal plays in neurodegenerative diseases such as Alzheimer's.⁷ Complexes with gallium(III) have been studied for use as potential radiopharmaceuticals,⁸ and the iron(III) complex was investigated as a water-soluble ferric iron source for the treatment of iron-deficiency anemia.⁹ Perhaps of greatest interest, the complex bis(maltolato)oxovanadium(IV) (BMOV)

has been extensively examined as an orally active insulin mimetic for the treatment of diabetes;^{10–13} bis(ethylmaltolato)oxovanadium(IV) (BEOV), a derivative of BMOV, is currently being evaluated in clinical trials.^{14,15}

Despite the wide-ranging interest in metal complexes of maltol, surprisingly few complexes based on heteroatom derivatives of maltol have been described. Most notably, the detailed coordination chemistry of the thio derivative of maltol, 3-hydroxy-2-methyl-4-thiopyrone (thiomaltol), and related compounds has been largely unexplored. Various reports of the synthesis of thiomaltol exist,^{16,17} along with a few reports of its use as an extractant for transition metals;^{18–21} however, these studies report little detailed

* Author to whom correspondence should be addressed. Tel: (858) 822-5596. Fax: (858) 822-5598. E-mail: scohen@ucsd.edu.

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characterization of the resulting coordination complexes.^{22–24} Herein, we report a single-step, high-yield synthesis of thiomaltol and the preparation of the iron(III) and nickel(II) coordination complexes of this intriguing ligand. The structures, spectroscopy, and electrochemical properties of these complexes are also described. The ligand is found to have a strong *trans* influence on the stereochemistry of the resulting metal complexes.^{25,26} Mixed O,S-donor ligands of this sort are expected to find utility in a variety of potential bioinorganic applications including use as medical chelators or in heavy metal waste remediation.

Experimental Section

General. Unless otherwise noted, starting materials were obtained from commercial suppliers (Aldrich) and used without further purification. 3-Hydroxy-4-pyrone (pyromeconic acid) was synthesized according to a literature procedure.²⁷ Elemental analysis was performed at the University of California, Berkeley Analytical Facility or Numea Resonance Labs, Inc. (San Diego, CA). ¹H/¹³C NMR spectra were recorded on a Varian FT-NMR spectrometer running at 300 or 400 MHz located in the Department of Chemistry and Biochemistry, University of California, San Diego. Gas chromatography electron impact mass spectrometry (GC–EIMS) was performed on a ThermoFinnigan Trace GC–MS, and electrospray ionization mass spectrometry (ESI–MS) was performed on either a ThermoFinnigan LCQ Advantage (quadrupole ion trap) or a Hewlett-Packard 5989B single-quadrupole mass spectrometer located in the Department of Chemistry and Biochemistry, University of California, San Diego. UV–visible spectra were recorded in methanol using a Hewlett-Packard 8452A spectrophotometer under PC control using the ChemStation software suite.

Thiomaltol (1). 3-Hydroxy-2-methyl-4-pyrone (maltol, 2.5 g, 19.9 mmol) was suspended in 125 mL of toluene and dissolved upon heating of the solution to ~100 °C. Hexamethyldisiloxane (HMDO, 5.4 g, 33.2 mmol) and P₄S₁₀ (1.6 g, 3.6 mmol) were added to the stirring solution. The reaction flask was protected from light with aluminum foil, fitted with a condenser, and heated to reflux under nitrogen for 7.5 h. A black precipitate was removed by vacuum filtration, and the filtrate was concentrated to give a dark brown solid. The product was purified by silica flash column chromatography eluting with 0–4% MeOH in CH₂Cl₂, as a bright yellow band. After removal of solvent on a rotary evaporator, an orange oil was isolated, which gave thiomaltol as orange needles upon storage at 4 °C. Yield: 70%. Mp 74–77 °C. ¹H NMR (CDCl₃, 300 MHz, 25 °C): δ 2.43 (s, 3H, –CH₃), 7.29 (d, *J* = 5.1 Hz, 1H, Ar–H), 7.55 (d, *J* = 5.1 Hz, 1H, Ar–H), 7.75 (br s, 1H, –OH). ¹³C NMR (CDCl₃, 100 MHz, 25 °C): δ 15.1 (–CH₃), 123.9 (Ar–C), 145.1 (Ar–C), 146.8 (Ar–C), 150.3 (Ar–C), 185.4 (C=S). GC–EIMS: *m/z* 141.9 [M•]⁺. Anal. Calcd for C₆H₆O₂S: C, 50.69; H, 4.25. Found: C, 50.32; H, 4.17.

Thiopyromeconic Acid (2). 3-Hydroxy-4-pyrone (pyromeconic acid, 0.5 g, 4.5 mmol) was suspended in 50 mL of CH₂Cl₂ and dissolved upon heating of the solution to ~50 °C. Hexamethyldisiloxane (HMDO, 1.2 g, 7.5 mmol) and P₄S₁₀ (0.4 g, 0.8 mmol) were added to the stirring solution. The reaction flask was protected from light with aluminum foil, fitted with a condenser, and heated to reflux under nitrogen for ~18 h. The bright orange solution was evaporated to dryness on a rotary evaporator to get an orange oil. The product was purified by silica flash column chromatography eluting with 1:1 hexanes:CH₂Cl₂, as a bright yellow fraction. After removal of solvent on a rotary evaporator the product was obtained as a yellow, crystalline solid. Yield: 70%. Mp 53 °C. ¹H NMR (CDCl₃, 400 MHz, 25 °C): δ 7.37 (d, *J* = 4.8 Hz, 1H, Ar–H), 7.60 (d, *J* = 5.2 Hz, 1H, Ar–H), 7.68 (s, 1H, –OH), 7.85 (s, 1H, Ar–H). ¹³C NMR (CDCl₃, 100 MHz, 25 °C): δ 124.7 (Ar–C), 133.4 (Ar–C), 147.6 (Ar–C), 152.7 (Ar–C), 187.8 (C=S). GC–EIMS: *m/z* 127.8 [M•]⁺. Anal. Calcd for C₅H₄O₂S: C, 46.86; H, 3.15. Found: C, 46.61; H, 3.40.

[Fe(thiomaltolato)₃] (3). Thiomaltol (60 mg, 0.42 mmol) was suspended in 5 mL of water. The ligand was dissolved by the addition of 42 μL of 10 M NaOH (1 equiv) producing a bright yellow solution. FeCl₃·6H₂O (38 mg, 0.14 mmol) was added to the reaction mixture, resulting in the formation of a black precipitate. The solution was placed under a nitrogen atmosphere and heated to reflux for ~0.5 h. Upon cooling, the solution was filtered through a fine glass frit and washed with ~20 mL of water to obtain a black powder. Yield: 71%. Mp 235 °C (dec). ESI–MS: *m/z* 337.8 [M – L]⁺, 143.0 [L + H]⁺; Anal. Calcd for C₁₈H₁₅O₆S₃Fe: C, 45.10; H, 3.15. Found: C, 45.17; H, 3.08.

[Ni(thiomaltolato)₂] (4). [Ni(thiomaltolato)₂] was synthesized by the same procedure used for [Fe(thiomaltolato)₃] starting from thiomaltol (50 mg, 0.35 mmol) and Ni(OAc)₂·2H₂O (43 mg, 0.17 mmol). The product was obtained as a maroon powder. Yield: 68%. Mp 230 °C (dec); ¹H NMR (CDCl₃, 400 MHz, 25 °C): δ 2.47 (s, 6H, –CH₃), 7.13 (d, *J* = 4.8 Hz, 2H, Ar–H), 7.51 (d, *J* = 4.8 Hz, 2H, Ar–H). ¹³C NMR (CDCl₃, 100 MHz, 25 °C): δ 15.4 (–CH₃), 119.6 (Ar–C), 143.6 (Ar–C), 152.4 (Ar–C), 164.2 (Ar–C), 178.8 (C=S). ESI–MS: *m/z* 341.0 [M + H]⁺. Anal. Calcd for C₁₂H₁₀O₄S₂Ni: C, 42.26; H, 2.96. Found: C, 41.96; H, 2.83.

X-ray Crystallographic Analysis. Single crystals of each compound suitable for X-ray diffraction structural determination were mounted on quartz capillaries by using Paratone oil and were cooled in a nitrogen stream on the diffractometer (–173 °C). Data were collected on a Bruker AXS area detector diffractometer. Peak integrations were performed with the Siemens SAINT software package. Absorption corrections were applied using the program SADABS. Space group determinations were performed by the program XPREP. The structures were solved by direct methods and refined with the SHELXTL software package.²⁸ All hydrogen atoms were fixed at calculated positions with isotropic thermal parameters unless otherwise noted; all non-hydrogen atoms were refined anisotropically.

Thiomaltol. Orange crystals of thiomaltol (1) suitable for X-ray diffraction structural determination were grown from cooling an oil of the compound containing small amounts of toluene, CH₂Cl₂, and methanol to 4 °C. No cocrystallized solvent molecules were found in the unit cell.

[Fe(thiomaltolato)₃]. Black crystals of [Fe(thiomaltolato)₃] (3) suitable for X-ray diffraction structural determination were grown from slow evaporation of a solution of the complex in acetone. No solvent molecules were found in the unit cell.

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Table 1. Crystal Data for Thiomaltol, [Fe(thiomaltolato)₃], and [Ni(thiomaltolato)₂]

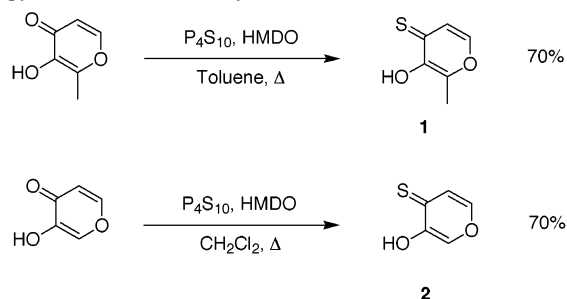
	thiomaltol	[Fe(thiomaltolato) ₃]	[Ni(thiomaltolato) ₂]
empirical formula	C ₆ H ₆ O ₂ S	C ₁₈ H ₁₅ O ₆ S ₃ Fe	C ₁₂ H ₁₄ O ₆ S ₂ Ni
temp, K	100(2)	100(2)	100(2)
crystal system	monoclinic	triclinic	orthorhombic
space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 1	<i>Pbcn</i>
unit cell dimens			
<i>a</i> , Å	5.3629(4)	8.5571(6)	22.928(15)
<i>b</i> , Å	8.6723(7)	12.8151(8)	6.6926(4)
<i>c</i> , Å	13.5524(11)	17.6321(11)	18.8132(13)
α, deg	90	83.965(1)	90
β, deg	99.858(1)	82.454(1)	90
γ, deg	90	81.990(1)	90
vol, Å ³	621.00(8)	1890.7(2)	2886.9(3)
<i>Z</i>	4	4	8
density (calcd), mg/m ³	1.521	1.684	1.735
crystal size, mm ³	0.49 × 0.33 × 0.15	0.34 × 0.19 × 0.13	0.35 × 0.24 × 0.03
θ range for data collection, deg	2.80–27.50	1.17–27.51	1.78–27.50
reflins collected	3780	12010	23027
indep reflns	1398 [<i>R</i> (int) = 0.0147]	8356 [<i>R</i> (int) = 0.0170]	3309 [<i>R</i> (int) = 0.0251]
data/restraints/params	1398/0/842	8356/0/511	3309/0/208
GOF on <i>F</i> ²	1.106	0.950	0.998
final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> 1 = 0.0312, <i>wR</i> 2 = 0.0880	<i>R</i> 1 = 0.0407, <i>wR</i> 2 = 0.0965	<i>R</i> 1 = 0.0288, <i>wR</i> 2 = 0.0812
<i>R</i> indices (all data)	<i>R</i> 1 = 0.0323, <i>wR</i> 2 = 0.0887	<i>R</i> 1 = 0.0538, <i>wR</i> 2 = 0.1005	<i>R</i> 1 = 0.0351, <i>wR</i> 2 = 0.0835
largest peak/hole difference, e Å ^{−3}	0.389 and −0.357	0.800 and −0.268	0.426 and −0.618

[Ni(thiomaltolato)₂]. Wine-red crystals of [Ni(thiomaltolato)₂] (**4**) suitable for X-ray diffraction structural determination were grown from slow evaporation of a solution of the complex in acetone. Two water molecules were found in the asymmetric unit; they are not coordinated to the nickel(II) ion. The water protons were found in the difference map, and their positions were refined.

Cyclic Voltammetry of Iron Complexes. Cyclic voltammetry experiments were performed by using a Bioanalytical Systems (BAS) CV-50W voltammetric analyzer under PC control. Solutions were prepared by dissolving ~10 mg of metal complex in CH₂Cl₂ containing 0.1 M *n*-Bu₄N(PF₆). The auxiliary and reference electrodes were a platinum wire and a silver electrode (Ag/AgCl_{aq}), respectively. A platinum electrode (BAS) was used for the working electrode. Samples were purged with N₂(g) for ~2 min before experiments were performed. Sweep rates were varied from 0.050 to 1.500 V/s in order to check the reversibility of the couple. Both [Fe(thiomaltolato)₃] and [Fe(maltolato)₃] showed reduced reversibility with increasing sweep rate. Therefore, data are reported at a sweep rate of 0.050 V/s at ambient temperature (~25 °C). The ferrocenium/ferrocene couple (Fc⁺/Fc⁰) was measured under identical conditions for use as a reference measurement (*E*_{1/2} = +0.471 V, Δ*E*_p = 0.127 V, 0.500 V/s); potentials are reported relative to Fc⁺/Fc⁰.

Results and Discussion

Several recent studies have demonstrated the utility of P₄S₁₀ in combination with hexamethyldisiloxane (HMDO) as an effective reagent for the thionation of esters, ketones, amides, and lactones.^{29–31} On the basis of these reports maltol was treated with P₄S₁₀ and HMDO in toluene and was heated to reflux (Scheme 1); purification of the product by flash silica column chromatography yielded an orange oil after removal of solvent that upon cooling to 4 °C generated thiomaltol (**1**) as analytically pure orange crystals in 70% yield. The generality of this approach was demonstrated by conversion of pyromeconic acid²⁷ (3-hydroxy-4-pyrone) to

Scheme 1. Synthesis of Thiomaltol from Maltol and Thiopyromeconic Acid from Pyromeconic Acid

thiopyromeconic acid (**2**) under similar conditions. In the synthesis of **2**, CH₂Cl₂ was used as the reaction solvent due to the extreme volatility of the thione product, which proved difficult to separate from higher boiling solvents such as toluene. Thiopyromeconic acid was isolated as a yellow solid in good yield. An earlier reported synthesis of thiomaltol utilized a similar approach to that presented here, but relied on multiple recrystallizations to obtain the pure product.¹⁶

An X-ray structure of the orange crystals of **1** unambiguously demonstrated that the material was thiomaltol (Table 1). The C–C bonds in the six-membered ring are not equivalent, with C1–C2 and C1–C6 bond lengths of ~1.43 Å and C2–C3 and C4–C6 bond lengths of ~1.35 Å, indicating that the latter two bonds have significantly more double-bond character (Figure 1). The C–S distance of 1.68 Å is indicative of the expected double bond.

Thiomaltol was complexed with iron(III) and nickel(II) under ambient, aerobic conditions (Scheme 2) in order to explore the coordination chemistry of this ligand with transition metal ions possessing distinctive coordination preferences. Addition of FeCl₃·6H₂O to an aqueous solution of thiomaltol instantly resulted in the formation of a black precipitate. Similarly, reaction of thiomaltol with Ni(OAc)₂·2H₂O generated a maroon precipitate. These complexes were stable to air and required no special handling. Single crystals of both complexes were obtained, and their structures were

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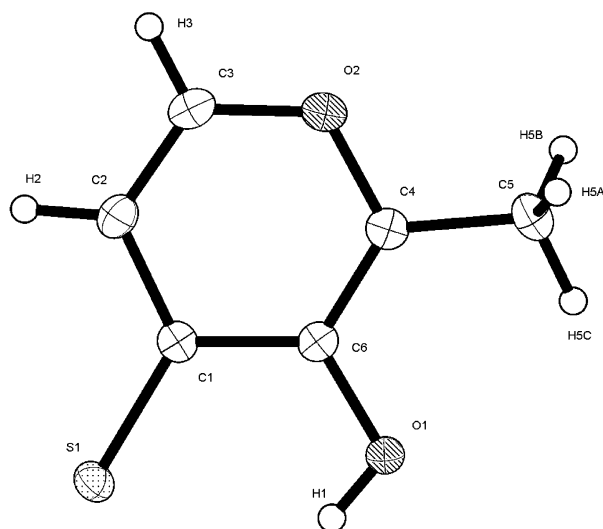
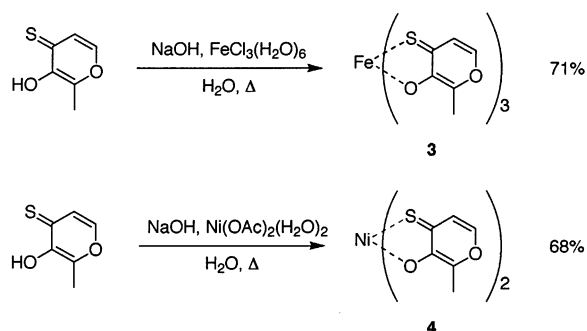


Figure 1. Structural diagram of thiomaltol (**1**) with atom-numbering scheme (ORTEP, 50% probability ellipsoids).

Scheme 2. Synthesis of Iron(III) and Nickel(II) Complexes with Thiomaltol



determined by X-ray diffraction (Table 1). The iron(III) complex **3** possesses the expected 6-coordinate, octahedral coordination geometry for a tris(chelate) complex (Figure 2). The average Fe–O and Fe–S bond lengths are 1.97 and 2.50 Å, respectively. The twist angle of **3** is 48.2° (60° for a perfect octahedron), slightly less than that reported for [Fe(maltolato)₃].⁹ Unlike the structure of the [Fe(maltolato)₃] and [Al(maltolato)₃] complexes,^{7,9} [Fe(thiomaltolato)₃] has a *fac* as opposed to *mer* geometry. Because the meridional geometry is statistically favored,⁹ this suggests that the thiomaltol ligand exhibits a substantial *trans* influence, thereby enforcing a facial geometry that is enthalpically favored. The *trans* influence is a thermodynamic trend whereby a strong ligand will arrange itself *trans* to a weaker ligand.^{25,26} The *trans* influence is distinct from the *trans* effect, the latter of which is a kinetic phenomenon and refers to rates of ligand substitution reactions.

The nickel(II) complex **4** has a 4-coordinate, *cis* square planar geometry (Figure 2). The *cis* geometry is again suggestive of a strong *trans* influence imposed by the thiomaltol ligand; however, no structure of [Ni(maltolato)₂] was available in the CCDC for comparison. However, the complexes [V=O(maltolato)₂], [Zn(maltolato)₂(H₂O)], and [Zn(maltolato)₂(H₂O)₂], where the two maltol ligands make up the square plane of either a square pyramidal or octahedral coordination geometry, all display *trans* orientations of the

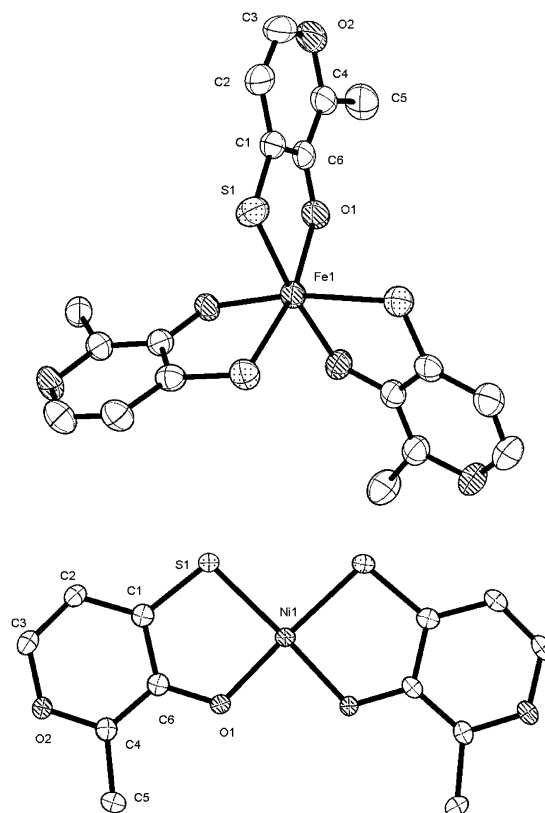


Figure 2. Structural diagram of [Fe(thiomaltolato)₃] (**3**, top) and [Ni(thiomaltolato)₂] (**4**, bottom) with partial atom-numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms and solvent molecules have been omitted for clarity.

maltol chelators.^{12,32} The average Ni–O and Ni–S bond distances in [Ni(thiomaltolato)₂] are 1.88 and 2.16 Å, respectively. The *cis* geometry causes a slight distortion in the square planar conformation, “opening” the S1–Ni–S2 angle to 92.41° while making the O1–Ni–O3 angle more acute at 86.83°.

Figure 3 shows the electronic absorption spectra for thiomaltol (**1**) and the metal complexes [Fe(thiomaltolato)₃] and [Ni(thiomaltolato)₂] in methanol. Thiomaltol has two major absorption bands at 276 and 358 nm, the latter of which gives the compound its characteristic orange color. Similarly, thiopyromeconic acid (**2**) has intense absorption bands at 272 and 354 nm. In the [Fe(thiomaltolato)₃] complex (**3**) four major bands are observed. The high-energy band is significantly more intense and is split into two transitions at 270 and 298 nm, with lower energy transitions at 368 and 510 nm. The broad transition at 510 nm is attributed to a LMCT process consistent with tris(chelate) iron(III) complexes of related ligands such as catecholates and hydroxypyridinones.^{33,34} The optical absorption spectrum of [Ni(thiomaltolato)₂] (**4**) is quite complicated with a broad (split less definitively than the transition in the same part of the iron(III) spectrum), intense absorption at 290 nm with a

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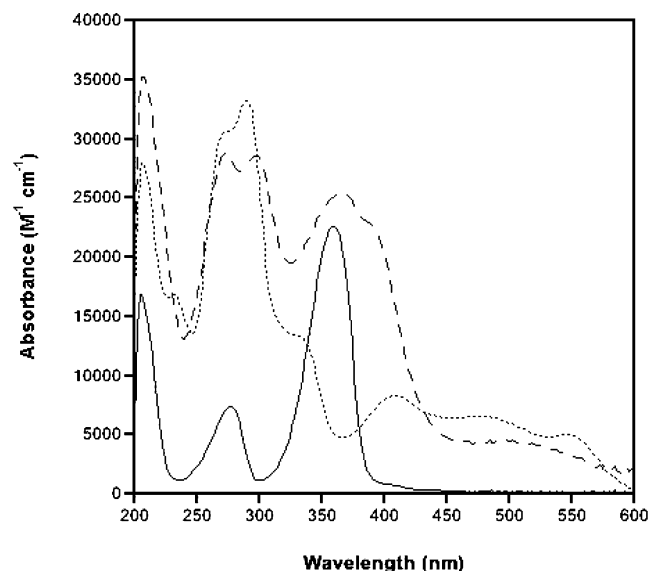


Figure 3. Absorbance spectra of thiomaltol (—), $[\text{Fe}(\text{thiomaltolato})_3]$ (---), and $[\text{Ni}(\text{thiomaltolato})_2]$ (···) in methanol.

shoulder at 332 nm and several weaker transitions at 408, 478, and 546 nm. The complexity of the $[\text{Ni}(\text{thiomaltolato})_2]$ electronic spectra is expected on the basis of studies of other square planar nickel(II) thiolate compounds where a number of bands are commonly observed due to d-d, LMCT, MLCT, and ligand-centered transitions.³³ Characteristic ligand-field transitions for square planar nickel(II) complexes are typically found between 400 and 555 nm ($\epsilon = 50\text{--}500 \text{ M}^{-1} \text{ cm}^{-1}$); although $[\text{Ni}(\text{thiomaltolato})_2]$ has an appropriate transition at 546 nm, the large extinction coefficient ($\epsilon = \sim 5000 \text{ M}^{-1} \text{ cm}^{-1}$) suggests that this band must be mixed with a substantial charge transfer component.³³ The electronic absorption spectra of thiomaltol and $[\text{Ni}(\text{thiomaltolato})_2]$ measured here are consistent with earlier descriptions of these compounds.²²

The electrochemistry of $[\text{Fe}(\text{thiomaltolato})_3]$ (**3**) was examined and compared with that of $[\text{Fe}(\text{maltolato})_3]$. Relative to ferrocene under the same conditions, $[\text{Fe}(\text{thiomaltolato})_3]$ showed a quasireversible redox couple (Figure 4) centered at -1.24 V ($\Delta E_p = 0.11 \text{ V}$) while that of $[\text{Fe}(\text{maltolato})_3]$ was -1.36 V ($\Delta E_p = 0.20 \text{ V}$). As anticipated, the softer O,S donor set of thiomaltol significantly stabilizes the ferrous ion relative to the harder maltol ligand.

Conclusions

In summary, the facile, high-yield syntheses of the interesting metal chelators thiomaltol and thiopyromeconic acid have been described. The crystal structures of thiomaltol and its iron(III) and nickel(II) metal complexes have been determined in order to probe the coordination chemistry of this ligand. These are the first structures of any thiomaltol metal complex, and the ligand is found to exert a strong *trans*

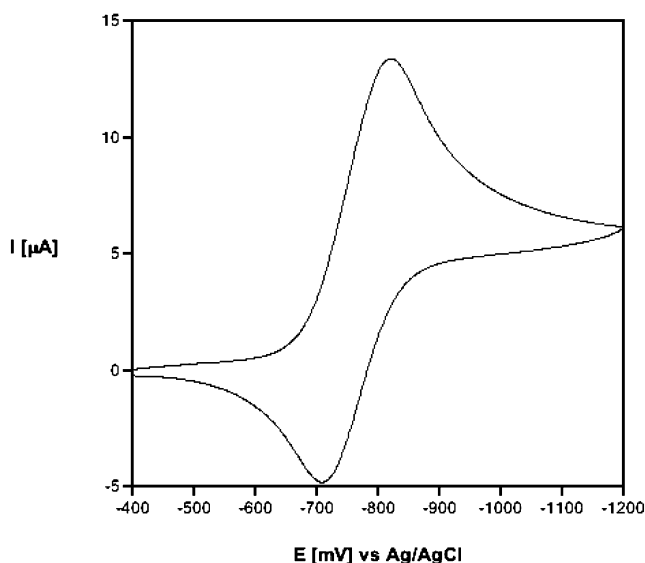


Figure 4. Cyclic voltammogram of $[\text{Fe}(\text{thiomaltolato})_3]$ in CH_2Cl_2 ($I = 0.1 \text{ M}$, scan rate = 50 mV s^{-1} , $T = 25^\circ \text{C}$).

influence on the stereochemistry of these compounds. In addition, the spectroscopic and electrochemical properties of these metal complexes have been investigated. Earlier studies have examined mixed O,S-donor ligands as metal chelators for use as sequestering agents for heavy metals such as lead(II).^{35–37} It is anticipated that thiomaltol, thiopyromeconic acid, and derivatives of these compounds may find potential utility as environmentally and medically useful heavy metal chelators.^{18,21} Investigations to test this hypothesis are presently underway.

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Supporting Information Available: X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>. X-ray crystallographic data is also available from the Cambridge Crystallographic Data Centre. Refer to CCDC reference numbers 210943, 210944, and 210945.

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