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Synthesis, structure and spectroscopy of new thiopyrone and hydroxypyridinethione transition-metal complexes†

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The coordination chemistry of several O,S mixed donor ligands, namely thiopyrone and hydroxypyridinethione chelators, with a variety of middle and late first-row transition-metal ions is described. Complexes of 3-hydroxy-2-methyl-4-thiopyrone (thiomaltol) with cobalt(II), copper(II) and zinc(II); 3-hydroxy-1,2-dimethyl-4(1*H*)-pyridinethione (3,4-HOPTO) with iron(III), nickel(II), copper(II) and zinc(II); and 3-hydroxy-1-methyl-2(1*H*)-pyridinethione (3,2-HOPTO) with iron(III), nickel(II), copper(II) and zinc(II) have been synthesized and characterized. The structures, absorbance spectroscopy, cyclic voltammetry and superconducting quantum interferometer device (SQUID) measurements of selected metal complexes, as well as ligand protonation constants, are reported. Most of the metal complexes show coordination geometries indicative of a strong *trans* influence by the O,S chelators. The data presented herein provide the most detailed study of the transition-metal coordination chemistry of both thiopyrone and hydroxypyridinethione O,S donor ligands to date, and provide the basis for the investigation of these ligands in realm of biological inorganic chemistry.

Introduction

Pyrones and hydroxypyridinones have been widely investigated in the bioinorganic community, particularly for use in medicinal applications. For example, 3-hydroxy-2-methyl-4-pyrone (maltol, Fig. 1) has been studied as a non-toxic, water-soluble iron(III) delivery agent for the treatment of iron-deficiency anemia.[1] The complex [Al(maltolato)$_3$] has been used to investigate how aluminum reaches the brain, which may be relevant to pathologies such as Alzheimer's disease.[2,3] Vanadyl (V=O) complexes of maltol-derived compounds have been extensively studied as promising leads for treating diabetes, because of their insulin-mimetic activity. Indeed, bis(ethylmaltolato)oxovanadium(IV) (BEOV) has reached clinical trials for the treatment of adult onset diabetes.[4–6] For hydroxypyridinones, compounds such as 1-methyl-3-hydroxy-2(1*H*)-pyridinone (3,2-HOPO) and 3-hydroxy-1,2-dimethyl-4(1*H*)-pyridinone (3,4-HOPO) and related derivatives have been examined as therapeutic chelating agents for iron overload[7–13] and aluminum toxicity.[14,15] Molybdenum complexes of both maltol and HOPO derivatives have shown protective ability for diabetic hearts.[16] Finally, complexes with technetium(V), rhenium(V), gallium(III), indium(III) and gadolinium(III) have been studied as radiopharmaceuticals and magnetic contrast agents for medical imaging.[17–20]

Despite the potentially far-reaching applications of pyrone and hydroxypyridinone chelators, few studies have been reported on the sulfur-containing analogues of these important metal chelators (Fig. 1). Extensive studies have been focused on the commercially available 1-hydroxypyridine-2(1*H*)-thione (1,2-HOPTO) and related compounds.[21–31] Some HOPTO and thiohydroxamate ligands have been proposed as iron sequestering agents based on siderophores, which are used by microbes for iron transport.[32–34] HOPOs and HOPTOs have been proposed to be therapeutic antioxidants for treating Alzheimer's disease.[35] Like their O,O donor analogues, thiopyrone and HOPTO complexes of vanadyl (V=O) and zinc(II) have been studied as insulin mimetics for treatment of diabetes,[36–38] and complexes with gallium(III) and indium(III) have been studied as radiopharmaceuticals for medical imaging.[22,39–42]

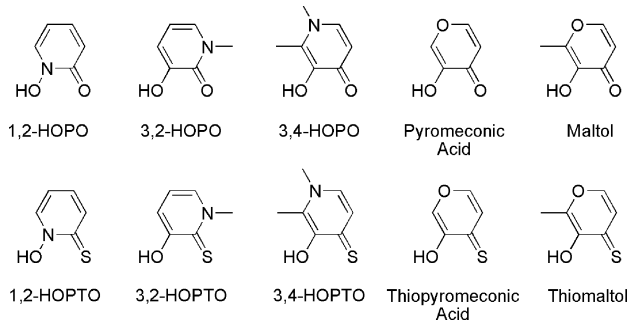

Fig. 1 List of pyrone, hydroxypyridinone (HOPO), thiopyrone and hydroxypyridinethione (HOPTO) compounds.

Recently, we and others have communicated some initial studies on the transition-metal chemistry of thiopyrones. Farmer and co-workers have suggested that metal complexes with sulfur-containing ligands, such as disulfiram and thiomaltol, may find application as melanoma-specific apoptosis inducers.[43,44] Orvig and co-workers have recently described the coordination chemistry of four thiopyrone and hydroxypyridinethione ligands with vanadyl, group 13 and lanthanide ions.[38,42] We have been primarily concerned with the use of these ligands as novel chelators for metalloprotein inhibition[45,46] and as potential heavy-metal sequestering agents.[47–50] Despite the growing interest in this class of ligands, very few elementary studies of their coordination chemistry or the characteristics of the resulting transition-metal complexes have been described.[51,52] Therefore, based on the potential medical and environmental applications of thiopyrones and hydroxypyridinethiones, we report herein on the basic coordination chemistry of these ligands with iron(III), cobalt(II), nickel(II), copper(II) and zinc(II). The protonation constants for thiomaltol, thiopyromeconic acid, 3,2-HOPTO and 3,4-HOPTO (Fig. 1) have been determined by spectrophotometric titrations. Spectroscopic, electrochemical, and magnetic properties of select complexes are discussed, which will contribute to expanding our fundamental knowledge about these important ligand systems.

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Experimental

General

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. The ligands 3-hydroxy-2-methyl-4-thiopyrone (thiomaltol), 3-hydroxy-4-thiopyrone (thiopyromeconic acid), 3-hydroxy-1,2-dimethyl-4(1*H*)-pyridinethione (3,4-HOPTO) and 3-hydroxy-1-methyl-2(1*H*)-pyridinethione (3,2-HOPTO) were synthesized as described.[50,51] Elemental analysis data were obtained through NuMega Resonance Labs, Inc. (San Diego, CA) or Robertson Microlit Laboratories (Madison, NJ). $^{1}H/^{13}C$ 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. Infrared spectra were collected on either a Nicolet AVATAR 320 FT-IR, Nicolet AVATAR 360 FT-IR, or a Perkin Elmer Spectrum One FT-IR instrument under PC control at the Department of Chemistry and Biochemistry, University of California, San Diego. UV-visible spectra were recorded in methanol or dimethyl sulfoxide (DMSO) using either a Hewlett-Packard 8452A spectrophotometer with the ChemStation software suite or a Perkin Elmer Lambda 25 spectrometer with the UVWinLab 4.2.0.0230 software package. Absorbance maxima are given as λ_{max}/nm (ε/M^{-1} cm^{-1}). Mass spectra were acquired at the Small Molecule Mass Spectrometry Facility located in the Department of Chemistry and Biochemistry, University of California, San Diego. A ThermoFinnigan LCQ-DECA mass spectrometer was used for the APCI analysis, and the data were analyzed using the Xcalibur software suite. A ThermoFinnigan MAT 900XL mass spectrometer was used to acquire the data for the high-resolution mass spectra (HRMS). The value Δ is the error in the measurement (in ppm), given by the equation $\Delta = [(M_E - M_T)/M_T] \times 10^6$, where M_E is the experimental mass and M_T is the theoretical mass. The HRMS result for [Zn(3,2-HOPTO)$_2$] was obtained with fast atom bombardment (FAB) as the ion source with 3-nitrobenzyl alcohol as the matrix and polyethylene glycol as a reference. The HRMS results for all other complexes were obtained with electron impact (EI) as the ion source and perfluorokerosene as the reference.

[Ni(maltolato)$_2$(H$_2$O)$_2$]. Maltol (100 mg, 0.79 mmol) was suspended in 3 mL of MeOH. The addition of 79 μL 10 M NaOH to the reaction flask produced a colorless solution. [Ni(OAc)$_2$]·4H$_2$O (99 mg, 0.39 mmol) was dissolved in 4 mL water, and added dropwise to the reaction flask to yield a transparent lime green solution. The flask was fitted with a reflux condenser under a dinitrogen atmosphere and heated to ~65 °C. Within 0.5 h, a green precipitate formed, which was collected by vacuum filtration with a fine glass frit, and washed with water. The product was dried in a vacuum oven with heat for ~12 h. Yield: 88%. Mp 227–232 °C. IR (neat, ATR): *ν* 833, 917, 1206, 1280, 1465, 1498, 1567 cm^{-1}. APCI-MS: *m*/*z* 308.94 [M + H]$^+$. EI-HRMS Calc. for $C_{12}H_{10}O_6Ni$: 307.9825. Found, Δ: 307.9828, 0.9 ppm. Anal. Calc. for $C_{12}H_{14}O_8Ni \cdot 0.25H_2O$: C, 41.25; H, 4.18. Found: C, 41.20; H, 3.84%.

[Co(thiomaltolato)$_2$]. Thiomaltol (100 mg, 0.70 mmol) was suspended in 4 mL of methanol and was dissolved by the addition of 70.0 μL of 10 M NaOH (~1 equiv.) producing a bright yellow solution. [CoCl$_2$]·6H$_2$O (84 mg, 0.35 mmol) was dissolved in 2 mL of water, and added dropwise to the reaction mixture resulting in the formation of a brown precipitate. The reaction flask was fitted with a condenser and was heated to reflux (~95 °C) under a dinitrogen atmosphere for 30 min. The solution was filtered utilizing a fine glass frit and washed with ~25 mL of water to obtain a brown powder. The powder was dried in a vacuum oven with heat for ~12 h. Yield: 80%. Mp 233–235 °C. IR (neat, ATR): *ν* 898, 1176 (C=S), 1217, 1279, 1408, 1480, 1567 cm^{-1}. UV-Vis in MeOH: 288 (22300), 395 (9000), 454 (5600). EI-HRMS: Calc. for $C_{12}H_{10}O_4S_2Co$: 340.9347. Found, Δ: 340.9343, −1.3 ppm.

[Cu(thiomaltolato)$_2$]. [Cu(thiomaltolato)$_2$] was synthesized by the same procedure used for [Co(thiomaltolato)$_2$] starting from thiomaltol (100 mg, 0.70 mmol) and [CuCl$_2$]·2H$_2$O (60 mg, 0.35 mmol). The product was a red–brown powder. Yield: 76%. Mp 224–227 °C (decomp.). IR (neat, ATR): *ν* 821, 902, 1182 (C=S), 1215, 1273, 1410, 1490, 1575 cm^{-1}. UV-Vis in MeOH: 269 (29000), 313 (27000), 389 (26700). APCI-MS: *m*/*z* 345.84 [M + H]$^+$. EI-HRMS: Calc. for $C_{12}H_{10}O_4S_2Cu$: 344.9311. Found, Δ: 344.9316, 1.5 ppm.

[Zn(thiomaltolato)$_2$]. [Zn(thiomaltolato)$_2$] was synthesized by the same procedure used for [Co(thiomaltolato)$_2$] starting from thiomaltol (100 mg, 0.70 mmol) and [Zn(OAc)$_2$]·2H$_2$O (77.0 mg, 0.35 mmol). The product was a yellow powder. Yield: 91%. Mp 265–268 °C (decomp.). ^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ 2.60 (s, 6H, CH$_3$), 7.56 (d, J = 4.5 Hz, 2H, Ar–H), 7.69 (d, J = 4.5 Hz, 2H, Ar–H). IR (neat, ATR): *ν* 801, 897, 1178 (C=S), 1226, 1293, 1409, 1479, 1572 cm^{-1}. UV-Vis in MeOH: 264 (15000), 303 (10400), 380 (23600). APCI-MS: *m*/*z* 346.88 [M + H]$^+$. Anal. Calc. for $C_{12}H_{10}O_4S_2Zn \cdot H_2O$: C, 39.41; H, 3.31. Found: C, 39.51; H, 2.96%.

[Fe(3,4-HOPTO)$_3$]. 3,4-HOPTO (50 mg, 0.32 mmol) was suspended in 3 mL of methanol and was dissolved by the addition of 32 μL of 10 M NaOH (~1 equiv.) and 5 mL of water producing a yellow solution. [FeCl$_3$]·6H$_2$O (29 mg, 0.11 mmol) was dissolved in 10 mL of water and was added dropwise to the reaction mixture resulting in the formation of a dark navy-blue precipitate. The reaction flask was covered in aluminum foil, fitted with a condenser and heated to reflux (~95 °C) under a dinitrogen atmosphere for 30 min. The solution was filtered through a fine glass frit and washed with ~40 mL of water to obtain a dark navy-blue powder. The product was dried in a vacuum oven with heat for ~12 h. Yield: 89%. Mp 312 °C (decomp.). IR (solid pellet with KBr): *ν* 818, 893, 943, 1194 (C=S), 1294, 1456, 1581 cm^{-1}. UV-Vis in DMSO: 352 (36800), 550 (4900). APCI-MS: *m*/*z* 365.49 [M − L + H]$^+$. Anal. Calc. for $C_{21}H_{24}N_3O_3S_3Fe \cdot H_2O$: C, 47.01; H, 4.88; N, 7.83. Found: C, 46.85; H, 4.75; N, 7.77%.

[Ni(3,4-HOPTO)$_2$]. [Ni(3,4-HOPTO)$_2$] was synthesized by the same procedure used for [Fe(3,4-HOPTO)$_3$] starting from 3,4-HOPTO (50 mg, 0.32 mmol) and [Ni(OAc)$_2$]·4H$_2$O (40 mg, 0.16 mmol). The product obtained was a bright orange powder. Yield: 95%. Mp > 315 °C. ^{1}H NMR (DMSO-d$_6$, 400 MHz, 25 °C): δ 2.33 (s, 6H, CH$_3$), 3.80 (s, 6H, NCH$_3$), 6.92 (d, J = 6.0 Hz, 2H, Ar–H), 7.29 (d, J = 6.4 Hz, 2H, Ar–H). IR (solid pellet with KBr): *ν*899, 1203 (C=S), 1294, 1462, 1587 cm^{-1}. UV-Vis in DMSO: 280 (44500), 314 (17000), 380 (6300), 426 (7500), 458 (6600). APCI-MS: *m*/*z* 367.53 [M + H]$^+$. Anal. Calc. for $C_{14}H_{16}N_2O_2S_2Ni$: C, 45.80; H, 4.39; N, 7.63. Found: C, 45.44; H, 4.57; N, 7.43%.

[Cu(3,4-HOPTO)$_2$]. [Cu(3,4-HOPTO)$_2$] was synthesized by the same procedure used for [Fe(3,4-HOPTO)$_3$] starting from 3,4-HOPTO (76 mg, 0.49 mmol) and [CuCl$_2$]·2H$_2$O (42 mg, 0.25 mmol). The product obtained was a brown powder. Yield: 86%. Mp 254–258 °C (decomp.). IR (neat, ATR): *ν* 787, 893, 949, 1165, 1200 (C=S), 1295, 1445, 1583 cm^{-1}. UV-Vis in DMSO: 292 (13900), 332 (21800), 372 (20800). APCI-MS: *m*/*z* 371.95 [M + H]$^+$. EI-HRMS: Calc. for $C_{14}H_{16}N_2O_2S_2Cu$: 370.9944. Found, Δ: 370.9945, 0.4 ppm.

[Zn(3,4-HOPTO)$_2$]. [Zn(3,4-HOPTO)$_2$] was synthesized by the same procedure used for [Fe(3,4-HOPTO)$_3$] starting from 3,4-HOPTO (76 mg, 0.49 mmol) and [Zn(OAc)$_2$]·2H$_2$O (54 mg, 0.25 mmol). The product obtained was an off-white powder. Yield: 90%. Mp 239–244 °C (decomp.). ^{1}H NMR (DMSO-d$_6$, 300 MHz, 25 °C): δ 2.46 (s, 6H, CH$_3$), 3.90 (s, 6H, NCH$_3$), 7.39 (d, J = 6.3 Hz, 2H, Ar–H), 7.50 (d, J = 6.6 Hz, 2H, Ar–H).

IR (solid pellet with KBr): *ν* 889, 945, 1109, 1199 (C=S), 1307, 1455, 1585 cm^{-1}. UV-Vis in DMSO: 290 (8400), 356 (35600). EI-HRMS: Calc. for $C_{14}H_{16}N_2O_2S_2Zn$: 371.9939. Found, *Δ*: 371.9951, 3.2 ppm.

[Fe(3,2-HOPTO)$_3$]. [Fe(3,2-HOPTO)$_3$] was synthesized by the same procedure used for [Fe(3,4-HOPTO)$_3$] starting from 3,2-HOPTO (100 mg, 0.70 mmol) and $[FeCl_3]\cdot 6H_2O$ (63 mg, 0.23 mmol). The product obtained was a dark navy-blue powder. Yield: 80%. Mp > 300 °C. IR (solid pellet with KBr): *ν* 732, 1044, 1131 (C=S), 1300, 1393, 1456, 1593 cm^{-1}. UV-Vis in DMSO: 376 (40400), 482 (6200), 584 (6300). EI-HRMS: Calc. for $C_{12}H_{12}N_2O_2S_2Fe$ $[ML_2]^-$: 335.9684. Found, *Δ*: 335.9688, 1.0 ppm.

[Ni(3,2-HOPTO)$_2$]. [Ni(3,2-HOPTO)$_2$] was synthesized by the same procedure used for [Fe(3,4-HOPTO)$_3$] starting from 3,2-HOPTO (30 mg, 0.21 mmol) and $[Ni(OAc)_2]\cdot 4H_2O$ (26 mg, 0.11 mmol). The product obtained was a bright orange powder. Yield: 65%. Mp > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C): *δ* 4.00 (s, 6H, CH_3), 6.78 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.02 (t, $J = 7.2$ Hz, 2H, Ar–H), 7.55 (d, $J = 6.4$ Hz, 2H, Ar–H). IR (neat, ATR): *ν* 786, 1041, 1123 (C=S), 1306, 1401, 1458, 1589 cm^{-1}. UV-Vis in DMSO: 312 (37000), 454 (26000). APCI-MS: m/z 338.97 $[M + H]^+$. Anal. Calc. for $C_{12}H_{12}N_2O_2S_2Ni$: C, 42.51; H, 3.57; N, 8.26. Found: C, 42.51; H, 3.34; N, 8.08%.

[Cu(3,2-HOPTO)$_2$]. [Cu(3,2-HOPTO)$_2$] was synthesized by the same procedure used for [Fe(3,4-HOPTO)$_3$] starting from 3,2-HOPTO (100 mg, 0.70 mmol) and $[CuCl_2]\cdot 2H_2O$ (60 mg, 0.35 mmol). The product obtained was an olive green powder. Yield: 97%. Mp 265–270 °C (decomp.). IR (neat, ATR): *ν* 765, 1045, 1127 (C=S), 1298, 1397, 1416, 1458, 1590 cm^{-1}. UV-Vis in DMSO: 326 (11200), 386 (34400). APCI-MS: m/z 343.88 $[M + H]^+$. Anal. Calc. for $C_{12}H_{12}N_2O_2S_2Cu$: C, 41.91; H, 3.52; N, 8.15. Found: C, 41.77; H, 3.53; N, 8.27%.

[Zn(3,2-HOPTO)$_2$]. [Zn(3,2-HOPTO)$_3$] was synthesized by the same procedure used for [Fe(3,4-HOPTO)$_3$] starting from 3,2-HOPTO (84 mg, 0.59 mmol) and $[Zn(OAc)_2]\cdot 2H_2O$ (66 mg, 0.30 mmol). The product obtained was an off-white powder. Yield: 88%. Mp 187–190 °C (decomp.). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C): *δ* 4.06 (s, 6H, CH_3), 6.90 (d, $J = 8.1$ Hz, 2H, Ar–H), 6.97 (t, $J = 7.0$ Hz, 2H, Ar–H), 7.70 (d, $J = 5.9$ Hz, 2H, Ar–H). IR (neat, ATR): *ν* 761, 1049, 1122 (C=S), 1290, 1336, 1416, 1458, 1593 cm^{-1}. UV-Vis in DMSO: 278 (12000), 362 (25500), 370 (26100). FAB-HRMS: Calc. for $C_{12}H_{13}N_2O_2S_2Zn$ $[M + H]^+$: 344.9704. Found, *Δ*: 344.9707, 0.8 ppm.

X-Ray crystallography

Single crystals of each compound suitable for X-ray diffraction structural determination (see ESI†) were mounted on quartz capillaries by using Paratone oil and were cooled in a nitrogen stream on the diffractometer. 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.[53] All hydrogen atoms were fixed at calculated positions with isotropic thermal parameters unless otherwise noted; all non-hydrogen atoms were refined anisotropically. The complexes [Cu(thiomaltolato)$_2$], [Ni(maltolato)$_2$(H_2O)$_2$], [Fe(3,4-HOPTO)$_3$] and [Zn(3,2-HOPTO)$_2$] all possess crystallographically imposed symmetry (see ESI† for details).

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See http://dx.doi.org/10.1039/b505034k for crystallographic data in CIF or other electronic format.

Cyclic voltammetry

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 ~10 mL CH_2Cl_2 containing 0.1 M *n*-$Bu_4N(PF_6)$. A platinum wire and a silver electrode ($Ag/AgCl_{aq}$) were used as the auxiliary and reference electrodes, respectively. A platinum electrode (BAS) was used for the working electrode. Samples were purged with N_2(g) for ~2 min before experiments were performed. Sweep rates were varied from 0.050 to 1.500 V s^{-1} in order to check the reversibility of the couple. The data are reported at a sweep rate of 0.050 V s^{-1} at ambient temperature (~25 °C). The ferrocenium–ferrocene couple (Fc^+/Fc^0) was measured under identical conditions for use as a reference measurement ($E_{1/2} = +0.473$ V, $\Delta E_p = 0.232$ V, 0.500 V s^{-1}); potentials are reported relative to Fc^+/Fc^0.

Magnetic measurements

Magnetic susceptibility measurements were performed on a Quantum Design model MPMS-5 SQUID magnetometer equipped with a 5.5 T superconducting magnet. The instrument operates in the 1.8–400 K temperature range. Variable-temperature dc susceptibility measurements were performed with an applied field of 1 T. The sample was immobilized in an eicosane matrix prior to measurement. The diamagnetic contributions from the sample container and eicosane were subtracted from the experimental data. Pascal's constants were also used to subtract the diamagnetic contributions, yielding paramagnetic susceptibilities.[54]

Spectrophotometric titrations

Measurements were performed with an Orion microcombination glass electrode. The electrode was calibrated for $-\log[H_3O^+]$ by titration of a standardized HCl solution (Aldrich, 0.1 M volumetric standard) with KOH (Aldrich, 0.1 M volumetric standard) at 25 °C and 0.1 M ionic strength (KCl) using a motorized burette (Dosimat, Metrohm, Switzerland) by adding a total of 50 aliquots of KOH under a N_2 atmosphere (solvent-vapor-saturated gas). The endpoint, electrode potential, and slope were determined by using Gran's method as implemented in the software GLEE.[55,56] The calibration procedure was repeated three times prior to each pK_a value determination. The electrode potential was measured with the Corning pH/Ion Analyzer 355, and the emf measurements were reproducible with ±0.1 mV accuracy.

All protonation constants reported in this study were determined using spectrophotometric measurements. The titrations were automated under PC control with programs written in Varian ADL language by Prof. Christoph J. Fahrni at the Georgia Institute of Technology. The UV/Vis absorption spectra of the ligands were monitored with a Varian Cary 50 Bio Spectrophotometer for a 3.0 mL solution of the corresponding ligand (~15 μM) in 0.1 M KCl under a dinitrogen atmosphere (solvent-vapor-saturated gas) titrated with 30–60 aliquots of KOH (0.66 mM) using a J-KEM Scientific syringe pump (Model 1250) and J-KEM Scientific Infinity Controller. Throughout the titration, the temperature was maintained at 25 ± 0.1 °C by circulating constant-temperature water through a jacketed titration cell. The emf of each solution was directly measured in the UV quartz cell (electrode diameter 3 mm) and converted to $-\log[H_3O^+]$ using the $E°$ and slope, as obtained from the electrode calibration procedure described above. The raw spectral and emf data were processed with nonlinear least-squares fit analysis using the SPECFIT (version 3.0.36) software package.[57]

Results and discussion

Synthesis

We recently reported the synthesis of several new O,S mixed ligands including thiopyrone and HOPTO chelators.[50,51] Pyrones were converted to thiopyrones using P_4S_{10} in combination with hexamethyldisiloxane in organic solvents.[51,58] The use of P_4S_{10} under solvent free conditions was found to smoothly convert hydroxypyridinones to the corresponding hydropyridinethiones in modest yields.[50] The general constitution of these compounds can be readily identified by their IR spectra. The sulfur substitution results in the expected $\nu_{C=S}$ stretching mode, which is found at lower wavenumbers (~1130–1200 cm^{-1}) relative to a normal $\nu_{C=O}$ band.[59] Reaction of these chelators with metal ion salts in mixed methanol–water solvent systems in the presence of stoichiometric base yielded the corresponding metal complexes in high yields. The complexes typically precipitate from solution and are isolated and purified by simple vacuum filtration followed by washing with copious amounts of deionized water. Metal complexes with thiomaltol, 3,4-HOPTO and 3,2-HOPTO are described below; complexes with thiopyromeconic acid were not investigated in detail, as they were anticipated to be essentially identical to those obtained with thiomaltol.

Structural characterization

Although the solubility of the metal complexes varied significantly, several complexes were sufficiently soluble to generate crystals for structural determination. The iron(III) and nickel(II) complexes of thiomaltol have been previously described.[51] The iron(III) complex demonstrated a pronounced *trans* influence with a *fac* arrangement of the ligands about the metal center. The *trans* influence is a thermodynamic effect where the strongest donor ligands arrange themselves *trans* to the weakest donor ligands (which consequently lengthens the weaker metal–ligand bond).[60,61] For a tris(chelate) complex with a nonsymmetric bidentate chelator, the *mer* geometry is statistically favored while the *fac* geometry is enthalpically favored.[61] The nickel(II) thiomaltol complex also showed a *trans* influence as demonstrated by the *cis* coordination geometry of the ligands in this square-planar complex.[51] This is in contrast to [Ni(maltolato)$_2$(H_2O)$_2$] which possesses a distorted octahedral geometry (Fig. 2) with the two maltol ligands forming a square plane and two water molecules occupying the axial positions (Table 1). In this complex the maltolato ligands have a *trans* geometry relative to each other and thus do not display a *trans* influence; the same stereochemistry is found in the complex [Zn(maltolato)$_2$(H_2O)$_2$].[62] The Ni–O bond lengths in [Ni(maltolato)$_2$(H_2O)$_2$] are nearly identical at 2.04 Å (Ni–O1) and 2.05 Å (Ni–O3) (Table 2).

In contrast to other O,S donor complexes, the structure of [Cu(thiomaltolato)$_2$] is rather surprising, showing a *trans* geometry (Fig. 2), and hence is inconsistent with the prominent *trans* influence observed with earlier reported complexes of this ligand[51] and related complexes reported here (*vide infra*). The copper(II) bond lengths are ~2.26 and ~1.93 Å for the Cu–S and Cu–O bonds, respectively. The structure is planar with O1–Cu–S1 (interligand) angles of 91.6°, close to the idealized value of 90° for a square-planar complex. The reasons why this complex does not show a geometry biased by the *trans* influence have not been resolved.

The structure of [Co(thiomaltolato)$_2$] reveals the expected tetrahedral geometry (Fig. 2). The geometry at the metal center is slightly distorted due to the substantially different Co–S *vs.* Co–O bond lengths at ~2.32 and ~1.95 Å, respectively. The O1–Co–O3 angle of 124.2° and the S1–Co–S2 angle of 123.5° are both greater than the expected 109.5° for an idealized tetrahedral geometry. As with [Co(thiomaltolato)$_2$], the structure of [Zn(thiomaltolato)$_2$] also shows a distorted tetrahedral coordination sphere (Fig. 2) due to the differing Zn–S and Zn–O bond lengths (Table 2), resulting in the

Table 1 X-ray data for [Ni(maltolato)$_2$(H_2O)$_2$], [Co(thiomaltolato)$_2$], [Cu(thiomaltolato)$_2$], [Zn(thiomaltolato)$_2$], [Fe(3,4-HOPTO)$_3$], [Ni(3,4-HOPTO)$_2$], [Cu(3,2-HOPTO)$_2$] and [Zn(3,2-HOPTO)$_2$]

Empirical formula	$NiC_{12}H_{26}O_{14}$	$CoC_{12}H_{10}O_4S_2$	$CuC_{12}H_{12}O_5S_2$	$ZnC_{12}H_{10}O_4S_2$	$FeC_{21}H_{24}N_3O_3S_3$	$NiC_{15}H_{30}N_2O_3S_2$	$CuC_{12}H_{12}N_2O_2S_2$	$ZnC_{12}H_{12}N_2O_2S_2$
T/K	273(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Rhombohedral	Orthorhombic	Monoclinic	Orthorhombic
Space group	*Pbca*, #61	$P2_1/c$, #14	$C2/c$, #15	$P2_1/c$, #14	$R\bar{3}c$, #161	*Pbca*, #61	$P2_1/n$, #14	*Fdd2*, #43
a/Å	4.8648(3)	7.4626(8)	8.1794(11)	7.4514(7)	15.6574(18)	7.4626(7)	7.0152(6)	25.738(3)
b/Å	16.7242(12)	23.583(3)	11.3535(15)	23.556(2)	15.6574(18)	19.3473(18)	14.9663(13)	8.2241(9)
c/Å	23.6399(17)	7.2977(8)	14.2539(19)	7.3272(7)	15.540(4)	22.730(2)	12.7659(11)	12.2965(14)
β/°	90	91.154(2)	96.253(2)	91.579(2)	90	90	105.9180(10)	90
V/Å^3, Z	1923.3(2), 4	1284.0(2), 4	1315.8(3), 4	1285.6(2), 4	3299.3(9), 6	3281.8(5), 8	1288.9(2), 4	2602.8(5), 8
D_c/Mg m^{-3}	1.565	1.765	1.837	1.796	1.566	1.616	1.772	1.765
Refl. collected	15280	10787	5413	8046	6528	26647	10823	5326
Independent reflections (R_{int})	2215 (0.0380)	2945 (0.0313)	1503 (0.0241)	2923 (0.0287)	1585 (0.0356)	3766 (0.0489)	2948 (0.0296)	1486 (0.0255)
Data/restraints/parameters	2215/0/176	2945/0/174	1503/0/94	2923/0/174	1585/1/96	3766/0/217	2948/0/174	1486/1/88
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0326$, $wR2 = 0.0665$	$R1 = 0.0640$, $wR2 = 0.1656$	$R1 = 0.0632$, $wR2 = 0.1556$	$R1 = 0.0356$, $wR2 = 0.0741$	$R1 = 0.0281$, $wR2 = 0.0608$	$R1 = 0.0462$, $wR2 = 0.0913$	$R1 = 0.0431$, $wR2 = 0.1068$	$R1 = 0.0321$, $wR2 = 0.0803$
R indices (all data)	$R1 = 0.0436$, $wR2 = 0.0703$	$R1 = 0.0717$, $wR2 = 0.1683$	$R1 = 0.0759$, $wR2 = 0.1629$	$R1 = 0.0418$, $wR2 = 0.0763$	$R1 = 0.0296$, $wR2 = 0.0612$	$R1 = 0.0634$, $wR2 = 0.0970$	$R1 = 0.0463$, $wR2 = 0.1085$	$R1 = 0.0327$, $wR2 = 0.0806$

Table 2 Summary of M–X bond lengths and observed stereochemical *trans* influence for chelate metal complexes presented

Compound	M–S/Å	M–O/Å	Coord. geometry, *trans* influence?
$[Ni(maltolato)_2(H_2O)_2]^a$	2.05 (M–O)	2.04	Octahedral, n/a
$[Fe(thiomaltolato)_3]^b$	2.50	1.97	*fac*-Octahedral, yes
$[Co(thiomaltolato)_2]$	2.32	1.95	Tetrahedral, n/a
$[Ni(thiomaltolato)_2]^b$	2.16	1.88	*cis*-Square-planar, yes
$[Cu(thiomaltolato)_2]$	2.26	1.93	*trans*-Square-planar, no
$[Zn(thiomaltolato)_2]$	2.32	1.96	Tetrahedral, n/a
$[Fe(3,4\text{-}HOPTO)_3]$	2.47	2.01	*fac*-Octahedral, yes
$[Ni(3,4\text{-}HOPTO)_2]$	2.15	1.88	*cis*-Square-planar, yes
$[Cu(3,2\text{-}HOPTO)_2]$	2.25	1.94	*cis*-Square-planar, yes
$[Zn(3,2\text{-}HOPTO)_2]$	2.31	1.96	Tetrahedral, n/a

[a] Ni–OH_2 2.08 Å. [b] From ref. 50.

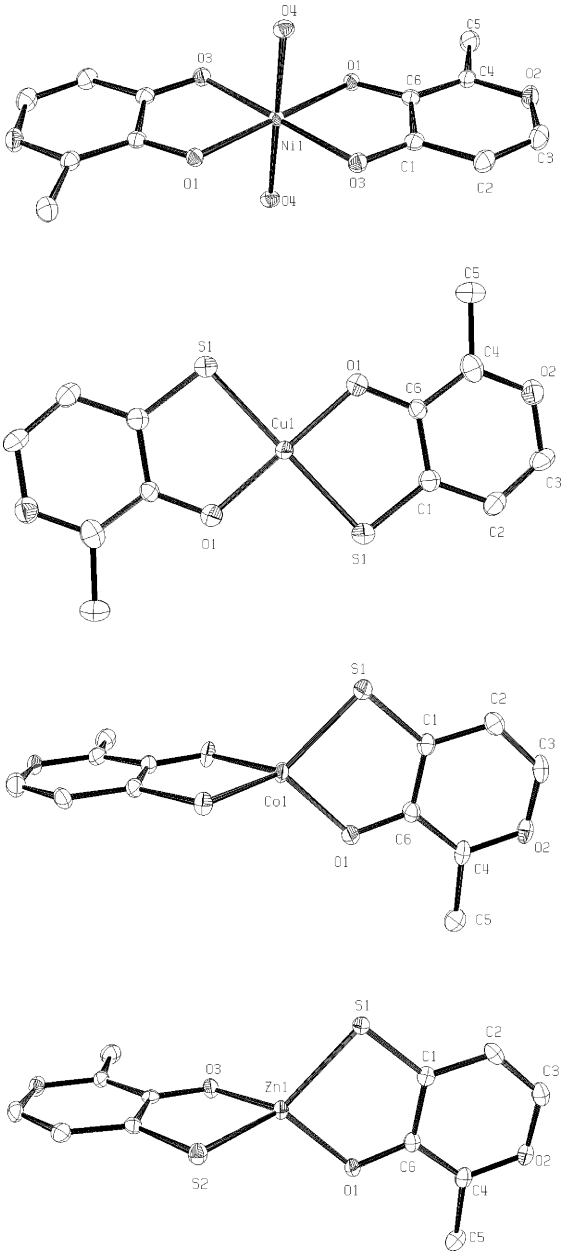

Fig. 2 Structural diagrams of (from top to bottom): $[Ni(maltolato)_2(H_2O)_2]$, $[Cu(thiomaltolato)_2]$, $[Co(thiomaltolato)_2]$ and $[Zn(thiomaltolato)_2]$ with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms and solvent molecules have been omitted for clarity.

O1–Zn–O3 angle of 119.9° and the S1–Zn–S2 angle of 125.4°. The $[Zn(thiomaltolato)_2]$ is distinct from the structurally characterized $[Zn(maltolato)_2(H_2O)_2]$, which is comprised of both six- and five-coordinate complexes.[62] Presumably the stronger donor ability of thiomaltol precludes the acquisition of additional solvent ligands in the solid state.

The structure of $[Fe(3,4\text{-}HOPTO)_3]$ shows a distorted octahedral geometry (Fig. 3), similar to $[Fe(thiomaltolato)_3]$, with a *fac* arrangement of the ligands, which reflects the strong *trans* influence of the 3,4-HOPTO ligand (Table 1).[51] The Fe–S bond length is ~2.47 Å while the Fe–O bond length is ~2.01 Å (Table 2). In addition, there are several similarities between the structures of $[Fe(3,4\text{-}HOPTO)_3]$ and $[Fe(3,4\text{-}HOPO)_3]$, including the similar twist angles of the metal centers (43.6 and 44.9°, respectively). Furthermore, $[Fe(3,4\text{-}HOPO)_3]$ also crystallizes as the *fac* isomer.[63,64] Indeed, several $[M(3,4\text{-}HOPO)_3]$ complexes have been found to crystallize as the *fac* isomer rather than the statistically favored *mer* isomer,[63–69] the latter of which is the commonly observed geometry of tris(maltolato) complexes.[1,2] The preference for the *fac* geometry in $[M(3,4\text{-}HOPO)_3]$ complexes, which were co-crystallized with 12 water molecules, may be due to the extensive hydrogen

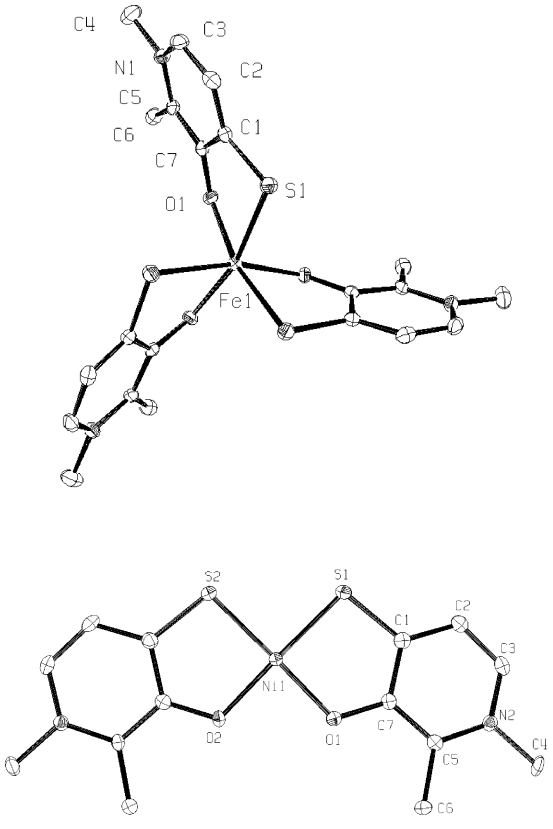

Fig. 3 Structural diagrams of $[Fe(3,4\text{-}HOPTO)_3]$ (top) and $[Ni(3,4\text{-}HOPTO)_2]$ (bottom) with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms have been omitted for clarity.

bonding reported in the crystal lattice of these compounds ($M = Al^{3+}$, Ga^{3+} and In^{3+}).[66,67] These [M(3,4-HOPO)$_3$] structures have been described as 'exoclathrates' where the metal complex is rigidly positioned outside the aquo hydrogen-bonded network.[70] Therefore, although [Fe(3,4-HOPTO)$_3$] and [Fe(3,4-HOPO)$_3$] have *fac* coordination spheres in the solid state, the 3,4-HOPO geometry is likely enforced by the extensive hydrogen bonding network, while the 3,4-HOPTO geometry originates from the *trans* influence of the O,S ligand (no solvent was co-crystallized with [Fe(3,4-HOPTO)$_3$]).

The [Ni(3,4-HOPTO)$_2$] complex shows the expected square-planar geometry (Fig. 3) with a *cis* coordination as predicted from a strong *trans* influencing ligand. The average Ni–S bond length is ~2.15 Å while the average Ni–O bond length is ~1.88 Å; these bond lengths are comparable to the corresponding [Ni(thiomaltolato)$_2$] complex (Table 2).[51] As with the analogous thiomaltol complex, the *cis* geometry causes a slight distortion in the square-planar conformation with the O,S chelators, making the O1–Ni–O2 slightly more acute at 88.4° while opening the S1–Ni–S2 angle to 91.1°. The complex exhibits little out-of-plane distortion with a mean deviation from the square plane (five atoms) of 0.01 Å. No structure of [Ni(3,4-HOPO)$_2$] is available for comparison in the Cambridge Crystallographic Data Center (CCDC); however, [Cu(3,4-HOPO)$_2$] and [Zn(3,4-HOPO)$_2$]·7H$_2$O both have two hydroxypyridinone ligands that make up the square plane of either a square-planar (Cu^{2+}) or distorted square-pyramidal coordination geometry (Zn^{2+}). In both cases the 3,4-HOPO chelators display a *trans* orientation relative to one another.[7,62] In contrast, the related nickel(II) complex with 1-hydroxy-6-methylpyridine-2(1*H*)-thione (a methyl-substituted derivative of 1,2-HOPTO, Fig. 1) and [Ni(thiomaltolato)$_2$] show square-planar geometries with a *cis* orientation of the ligands, as expected from a strong *trans* influencing O,S ligand.[24]

Fig. 4 shows the structure of [Cu(3,2-HOPTO)$_2$], which has a distorted square-planar geometry (Table 1). There was no structure of the corresponding 3,2-HOPO metal complex in the CCDC for comparison. The related copper(II) complex with 1-hydroxy-6-methylpyridine-2(1*H*)-thione has a distorted square-pyramidal geometry with the O,S ligands in a *cis* configuration and the copper centers weakly bridged by *N*-oxide oxygen atoms.[24] The bond lengths in [Cu(3,2-HOPTO)$_2$] are comparable to the corresponding thiomaltol complexes (Table 2); however, unlike [Cu(thiomaltolato)$_2$], the 3,2-HOPTO complex shows a *trans* influence with the corresponding *cis* coordination geometry. Similar to other square-planar structures with O,S ligands, [Cu(3,2-HOPTO)$_2$] shows a distortion of the square-planar structure due to the *cis* geometry with an opening of the S1–Cu–S2 angle to 94.2° and a O1–Cu–O2 angle of 92.4°. The ligands are twisted from an idealized square plane with an RMS deviation from the plane (five atoms) of 0.17 Å. The structure of [Cu(3,2-HOPTO)$_2$] further highlights the anomalous *trans* conformation of [Cu(thiomaltolato)$_2$] relative to other square-planar complexes with the O,S ligands examined in this study. This suggests that the energy difference between the *cis* and *trans* conformation in the copper(II) complexes is small, and only a weak *trans* influence is present.

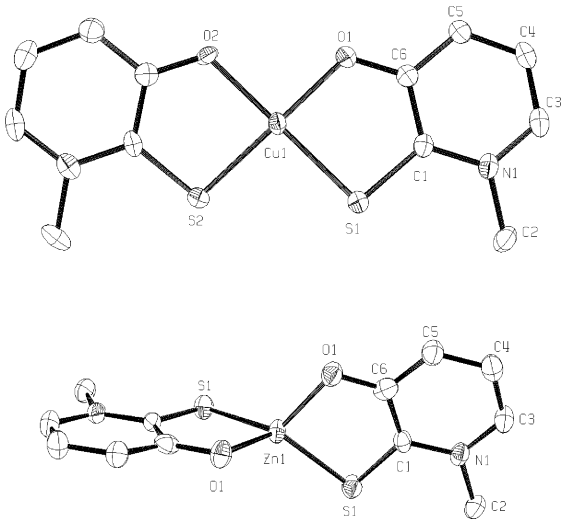

Fig. 4 Structural diagrams of [Cu(3,2-HOPTO)$_2$] (top) and [Zn(3,2-HOPTO)$_2$] (bottom) with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms have been omitted for clarity.

The [Zn(3,2-HOPTO)$_2$] complex (Fig. 4), due to the substantially different M–S and M–O bond lengths (Table 2), possesses a distorted tetrahedral coordination sphere as in the other tetrahedral complexes described here. The structure of the corresponding 3,2-HOPO metal complex is not available in the CCDC for comparison; however, the related 1-hydroxy-6-methylpyridine-2(1*H*)-thione complex with zinc(II) has a similar distorted tetrahedral geometry.[24] As described with other O,S ligands and as expected based on ionic radii, the order of metal–donor atom distances in the ML_2 structures presented here is $Ni^{2+} < Cu^{2+} < Co^{2+} \approx Zn^{2+}$.[71]

UV-visible spectroscopy

With the exception of the closed shell zinc(II) complexes, the metal complexes described here possessed a range of deep colors from the reddish-brown [Cu(thiomaltolato)$_2$] to the dark navy blue [Fe(3,2-HOPTO)$_3$]. Due to the varied solubility of the metal complexes, the electronic spectra of the compounds were recorded in either methanol (thiomaltol) or DMSO (3,2-HOPTO, 3,4-HOPTO). The results of these measurements are summarized in Table 3 and illustrated in Fig. 5. Typical ligand centered transitions are observed in the high energy region of these absorption spectra. In addition, the iron(III) and cobalt(II) complexes show broad charge transfer transitions

Table 3 Summary of UV-visible absorption features for the coordination complexes described in this report

Compound	λ_{max}/nm (ε/M^{-1} cm^{-1})
[Co(thiomaltolato)$_2$][a]	288 (22300), 395 (9000), 454 (5600)
[Cu(thiomaltolato)$_2$][a]	269 (29000), 313 (27000), 389 (26700)
[Zn(thiomaltolato)$_2$][a]	264 (15000), 303 (10400), 380 (23600)
[Fe(3,4-HOPTO)$_3$][b]	352 (36800), 550 (4900)
[Ni(3,4-HOPTO)$_2$][b]	280 (44500), 314 (17000), 380 (6300), 426 (7500), 458 (6600)
[Cu(3,4-HOPTO)$_2$][b]	292 (13900), 332 (21800), 372 (20800)
[Zn(3,4-HOPTO)$_2$][b]	290 (8400), 356 (35600)
[Fe(3,2-HOPTO)$_3$][b]	376 (40400), 482 (6200), 584 (6300)
[Ni(3,2-HOPTO)$_2$][b]	312 (37000), 454 (26000)
[Cu(3,2-HOPTO)$_2$][b]	326 (11200), 386 (34400)
[Zn(3,2-HOPTO)$_2$][b]	278 (12000), 362 (25500), 370 (26100)

[a] Obtained in MeOH. [b] Obtained in DMSO.

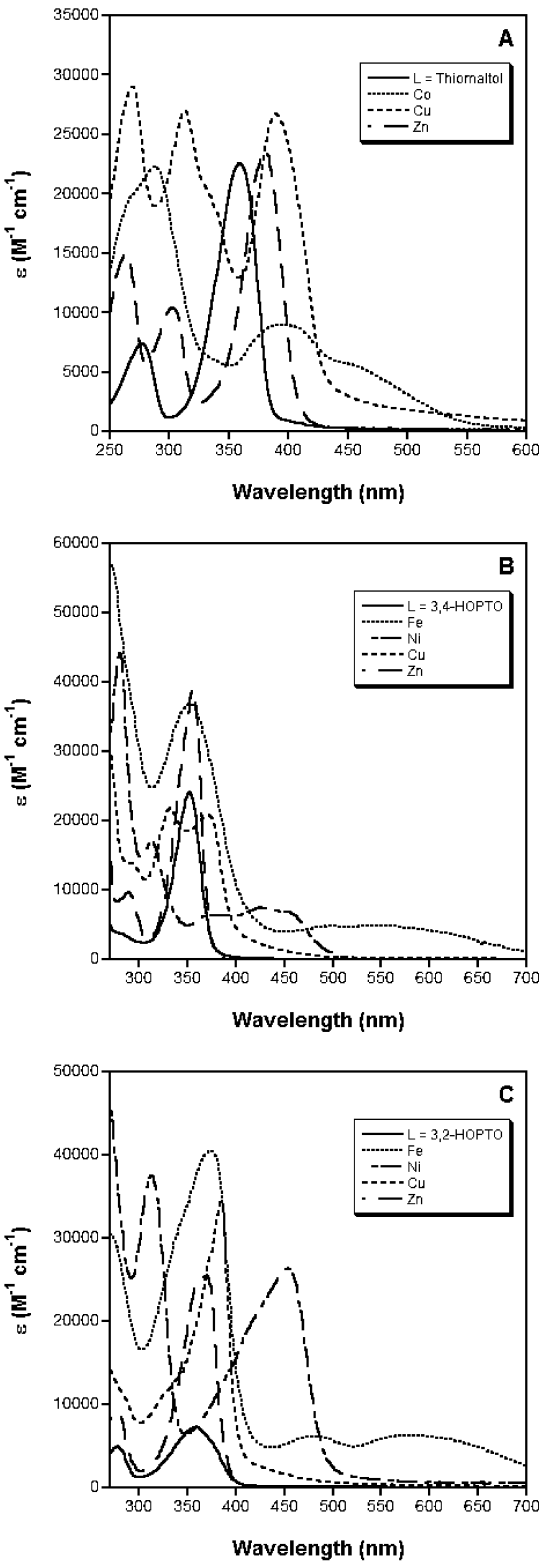

Fig. 5 Absorbance spectra of O,S ligands and coordination complexes: (A) thiomaltol (solid line), [Co(thiomaltolato)$_2$] (dotted line), [Cu(thiomaltolato)$_2$] (narrow dashed line) and [Zn(thiomaltolato)$_2$] (wide dashed line) in methanol; (B) 3,4-HOPTO (solid line), [Fe(3,4-HOPTO)$_3$] (dotted line), [Ni(3,4-HOPTO)$_2$] (dashed-dotted line), [Cu(3,4-HOPTO)$_2$] (narrow dashed line) and [Zn(3,4-HOPTO)$_2$] (wide dashed line) in DMSO; (C) 3,2-HOPTO (solid line), [Fe(3,2-HOPTO)$_3$] (dotted line), [Ni(3,2-HOPTO)$_2$] (dashed-dotted line), [Cu(3,2-HOPTO)$_2$] (narrow dashed line) and [Zn(3,2-HOPTO)$_2$] (wide dashed line) in DMSO.

in the visible part of the spectrum, which is characteristic of related complexes formed with catecholates, pyrones and hydroxypyridinonates.[51,72,73]

Electrochemistry

The cyclic voltammetry of [Fe(thiomaltolato)$_3$] has been reported.[51] Relative to ferrocene under the same conditions, [Cu(thiomaltolato)$_2$] and [Cu(3,2-HOPTO)$_2$] (Fig. S1, ESI†) showed quasireversible redox couples centered at −1.16 V ($\Delta E_p = 0.18$ V) and at −1.28 V ($\Delta E_p = 0.18$ V), respectively. Both [Cu(thiomaltolato)$_2$] and [Cu(3,2-HOPTO)$_2$] showed reduced reversibility with increasing sweep rate. The electrochemistry of the analogous O,O copper(II) complexes has not been reported.

Magnetic measurements

Both the [Fe(3,4-HOPTO)$_3$] and the [Fe(3,2-HOPTO)$_3$] complexes have magnetic properties typical of a mononuclear high-spin ($S = 5/2, g = 2$) iron(III) ion. The theoretical spin only value of 5.92 μ_B is in good agreement with the experimental room temperature moment of 5.9 μ_B from the SQUID experiments (Fig. S2, ESI†). The high-spin ground state of these complexes is consistent with early findings that [Fe(thiohydroxamato)$_3$] complexes are high-spin; these [Fe(thiohydroxamato)$_3$] tris(chelate) complexes were found to be surprisingly stable toward Δ-/Λ-interconversion for a high-spin iron(III) complex.[32,33]

Ligand protonation constants

The protonation equilibria of the O,S donor ligands were investigated by spectrophotometric titrations. The pK_a values were determined by titrating a solution of each ligand in water (~15 μM) with KOH at a constant ionic strength (Fig. S3, ESI†). The experimentally measured potential data were converted to −log[H_3O^+] values based on the electrode potential ($E°$) and slope, which were obtained from the electrode calibration data using Gran's method.[56,74] The corresponding pK_a values were determined using a nonlinear least-squares fit analysis (Table 4).[55,75] The ligands show one protonation event, which can be assigned to the hydroxyl group of each compound. The data show that, in general, the O,S donor ligands are more acidic than their O,O counterparts. This is the expected trend because sulfur is less electronegative and more polarizable than oxygen, which should increase delocalization into the aromatic heterocycle and thereby stabilize the negative charge after deprotonation of the hydroxyl oxygen. This effect appears to be attenuated in the 3,2-HOPTO isomer, which has a pK_{a1} value that is slightly higher than that of 3,2-HOPO. The thiopyrones are found to be more acidic than 3,4-HOPTO or 3,2-HOPTO; this is because the more electronegative ring oxygen atoms stabilize the deprotonated form of the thiopyrones more effectively than does the ring nitrogen atom of the HOPTOs. While this manuscript was in preparation, Orvig and co-workers reported the protonation constants for thiomaltol and 3,4-HOPTO as determined by potentiometry;[42] their findings are wholly consistent with the values reported in Table 4.

In summary, the coordination chemistry of thiomaltol, 3,4-HOPTO and 3,2-HOPTO ligands with iron(III), cobalt(II), nickel(II), copper(II) and zinc(II) ions has been studied by

Table 4 Protonation constants for thiomaltol, thiopyromeconic acid, 3,4-HOPTO and 3,2-HOPTO and for their corresponding O,O analogs in aqueous solution

Ligand (O,S)	pK_a Value[a]	Ligand (O,O)	pK_a Value
Thiomaltol	8.16(2)	Maltol	8.513(2)[a,c]
Thiopyromeconic acid	7.29(5)	Pyromeconic acid	7.69(3)[b]
3,4-HOPTO	9.47(2)	3,4-HOPO	9.77(1)[a,d]
3,2-HOPTO	8.97(5)	3,2-HOPO	8.89(1)[a,e]

[a] $I = 0.10$ M KCl, $T = 25$ °C. [b] $I = 0.5$ M, $T = 25$ °C, ref. 75. [c] Ref. 76. [d] Ref. 77. [e] Ref. 78.

crystallographic, spectroscopic, electrochemical and SQUID experiments. Structural characterization of the homoleptic complexes shows the presence of a strong *trans* influence, with few exceptions. Spectrophotometric titrations have been performed on thiopyrone and HOPTO ligands, showing that they are generally more acidic than their O,O analogues. These findings are the first extensive characterization of transition-metal complexes of these ligands, which is a fundamental step for considering their use in medicinal and environmental bioinorganic chemistry. We are continuing our investigations into the use of these sulfur-containing ligands for a variety of applications from sequestering heavy metals to use as chelators in metalloenzyme inhibitors.[46,50]

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References

1 M. T. Ahmet, C. S. Frampton and J. Silver, *J. Chem. Soc., Dalton Trans.*, 1988, 1159.
2 M. M. Finnegan, S. J. Rettig and C. Orvig, *J. Am. Chem. Soc.*, 1986, **108**, 5033.
3 P. Yu, B. L. Phillips, M. M. Olmstead and W. H. Casey, *J. Chem. Soc., Dalton Trans.*, 2002, 2119.
4 M. Melchior, S. J. Rettig, B. D. Liboiron, K. H. Thompson, V. G. Yuen, J. H. McNeill and C. Orvig, *Inorg. Chem.*, 2001, **40**, 4686.
5 K. H. Thompson and C. Orvig, *Met. Ions Biol. Syst.*, 2004, **41**, 221.
6 T. Storr, D. Mitchell, P. Buglyó, K. H. Thompson, V. G. Yuen, J. H. McNeill and C. Orvig, *Bioconjugate Chem.*, 2003, **14**, 212.
7 A. El-Jammal, P. L. Howell, M. A. Turner, N. Li and D. M. Templeton, *J. Med. Chem.*, 1994, **37**, 461.
8 R. C. Scarrow, P. E. Riley, K. Abu-Dari, D. L. White and K. N. Raymond, *Inorg. Chem.*, 1985, **24**, 954.
9 R. C. Scarrow and K. N. Raymond, *Inorg. Chem.*, 1988, **27**, 4140.
10 M. Streater, P. D. Taylor, R. C. Hider and J. Porter, *J. Med. Chem.*, 1990, **33**, 1749.
11 B. L. Rai, L. S. Dekhordi, H. Khodr, Y. Jin, Z. Liu and R. C. Hider, *J. Med. Chem.*, 1998, **41**, 3347.
12 Z. D. Liu, H. H. Khodr, D. Y. Liu, S. L. Lu and R. C. Hider, *J. Med. Chem.*, 1999, **42**, 4814.
13 S. M. Cohen, B. O'Sullivan and K. N. Raymond, *Inorg. Chem.*, 2000, **39**, 4339.
14 R. A. Yokel, A. K. Datta and E. G. Jackson, *J. Pharmacol. Exp. Ther.*, 1991, **257**, 100.
15 D. D. Allen, C. Orvig and R. A. Yokel, *Toxicology*, 1994, **92**, 193.
16 S. J. Lord, N. A. Epstein, R. L. Paddock, C. M. Vogels, T. L. Hennigar, M. J. Zaworotko, N. J. Taylor, W. R. Driedzic, T. L. Broderick and S. A. Westcott, *Can. J. Chem.*, 1999, **77**, 1249.
17 H. Luo, S. J. Rettig and C. Orvig, *Inorg. Chem.*, 1993, **32**, 4491.
18 M. M. Finnegan, T. G. Lutz, W. O. Nelson, A. Smith and C. Orvig, *Inorg. Chem.*, 1987, **26**, 2171.
19 B. L. Ellis, A. K. Duhme, R. C. Hider, M. B. Hossain, S. Rizvi and D. van der Helm, *J. Med. Chem.*, 1996, **39**, 3659.
20 S. M. Cohen, J. Xu, E. Radkov, K. N. Raymond, M. Botta, A. Barge and S. Aime, *Inorg. Chem.*, 2000, **39**, 5747.
21 Y.-P. Fang, C.-L. Chen, X.-J. Wang, B.-S. Kang, K. Yu and C.-Y. Su, *Acta. Crystallogr., Sect. E*, 2002, **58**, m480.
22 A. Rodríguez, J. Romero, J. A. García-Vázquez, A. Sousa, J. Zubieta, D. J. Rose and K. Maresca, *Inorg. Chim. Acta*, 1998, **281**, 70.
23 A. D. Bond, N. Feeder, S. J. Teat and W. Jones, *Acta. Crystallogr., Sect. C*, 2001, **57**, 1157.
24 D. X. West, C. A. Brown, J. P. Jasinski, J. M. Jasinski, R. M. Heathwaite, D. G. Fortier, R. J. Staples and R. J. Butcher, *J. Chem. Crystallogr.*, 1998, **28**, 853.
25 D. X. West, J. L. Hines, R. K. Bunting, M. C. R. Symons and N. A. Malik, *Inorg. Chim. Acta*, 1988, **143**, 229.
26 J.-C. Shi, T.-B. Wen, Y. Zheng, S.-J. Zhong, D.-X. Wu, Q.-T. Liu, B.-S. Kang, B.-M. Wu and T. C. W. Mak, *Polyhedron*, 1997, **16**, 369.
27 T.-B. Wen, J.-C. Shi, Q.-T. Liu, B.-S. Kang, B.-M. Wu and T. C. W. Mak, *Acta. Crystallogr., Sect. C*, 1996, **52**, 1204.
28 Y.-J. Xu, B.-S. Kang, X.-T. Chen and L.-R. Huang, *Acta. Crystallogr., Sect. C*, 1995, **51**, 370.
29 J. Sanmartín, M. R. Bermejo, J. A. García-Vázquez, J. Romero and A. Sousa, *Transition Met. Chem. (Weinheim)*, 1993, **18**, 528.
30 V. Manivannan, S. Dutta, P. Basu and A. Chakravorty, *Inorg. Chem.*, 1993, **32**, 769.
31 M. A. Robinson, *J. Inorg. Nucl. Chem.*, 1964, **26**, 1277.
32 K. Abu-Dari and K. N. Raymond, *J. Am. Chem. Soc.*, 1977, **99**, 2003.
33 K. Abu-Dari and K. N. Raymond, *Inorg. Chem.*, 1977, **16**, 807.
34 K. Abu-Dari and K. N. Raymond, *Inorg. Chem.*, 1991, **30**, 519.
35 G. S. Tilbrook, R. C. Hider and M. Y. Moridani, in *Therapeutic Antioxidants for Alzheimer's Disease*, WO9825905, 1998.
36 H. Sakurai, H. Sano, T. Takino and H. Yasui, *J. Inorg. Biochem.*, 2000, **80**, 99.
37 A. Katoh, T. Tsukahara, R. Saito, K. K. Ghosh, Y. Yoshikawa, Y. Kojima, A. Tamura and H. Sakurai, *Chem. Lett.*, 2002, 114.
38 V. Monga, K. H. Thompson, V. G. Yuen, V. Sharma, B. O. Patrick, J. H. McNeill and C. Orvig, *Inorg. Chem.*, 2005, **44**, 2678.
39 D. J. Rose, Y. D. Chang, Q. Chen, P. B. Kettler and J. Zubieta, *Inorg. Chem.*, 1995, **34**, 3973.
40 C. S. John, C. H. Paik, S. Kinuya, J. G. McAfee, R. D. Neumann and R. C. Reba, *J. Nucl. Med.*, 1991, **32**, 1090.
41 D. A. Moore, R. J. Motekaitis, A. E. Martell and M. J. Welch, *J. Nucl. Med.*, 1989, **30**, 922.
42 V. Monga, B. O. Patrick and C. Orvig, *Inorg. Chem.*, 2005, **44**, 2666.
43 D. Cen, D. Brayton, B. Shahandeh, F. L. Meyskens, Jr. and P. J. Farmer, *J. Med. Chem.*, 2004, **47**, 6914.
44 P. J. Farmer and D. F. Brayton, *Poster #672 (INOR)*, 227th ACS National Meeting, Anaheim,CA, 2004.
45 D. T. Puerta and S. M. Cohen, *Inorg. Chem.*, 2003, **42**, 3423.
46 D. T. Puerta, J. A. Lewis and S. M. Cohen, *J. Am. Chem. Soc.*, 2004, **126**, 8388.
47 E. Uhlemann, H. Motzny and G. Wilke, *Z. Anorg. Allg. Chem.*, 1973, **401**, 255.
48 B. Schuknecht, E. Uhlemann and G. Wilke, *Z. Chem.*, 1975, **15**, 285.
49 E. Uhlemann, W. Bechmann and E. Ludwig, *Anal. Chim. Acta*, 1978, **100**, 635.
50 J. A. Lewis and S. M. Cohen, *Inorg. Chem.*, 2004, **43**, 6534.
51 J. A. Lewis, D. T. Puerta and S. M. Cohen, *Inorg. Chem.*, 2003, **42**, 7455.
52 D. Rehorek, P. Thomas and E. Uhlemann, *Z. Chem.*, 1973, **13**, 23.
53 G. M. Sheldrick, in *SHELXTL version 5.1 Software Reference Manual*, Madison, WI, 1997.
54 O. Kahn, *Molecular Magnetism*, Wiley-VCH Inc., New York, 1993.
55 A. E. Martell and R. J. Motekaitis, *Determination and Use of Stability Constants*, VCH Publishers, Inc., New York, 1988.
56 P. Gans and B. O'Sullivan, *Talanta*, 2000, **51**, 33.
57 R. A. Binstead, A. D. Zuberbuhler and B. Jung, in *SPECFIT Global Analysis System*, Marlborough, MA, 2004.
58 T. J. Curphey, *J. Org. Chem.*, 2002, **67**, 6461.
59 E. Spinner, *J. Org. Chem.*, 1958, **23**, 2037.
60 T. G. Appleton, H. C. Clark and L. E. Manzer, *Coord. Chem. Rev.*, 1973, **10**, 335.
61 E. J. Enemark and T. D. P. Stack, *Angew. Chem., Int. Ed.*, 1995, **34**, 996.
62 S. I. Ahmed, J. Burgess, J. Fawcett, S. A. Parsons, D. R. Russell and S. H. Laurie, *Polyhedron*, 2000, **19**, 129.
63 J. Charalambous, A. Dodd, M. McPartlin, S. O. C. Matondo, N. D. Pathirana and H. R. Powell, *Polyhedron*, 1988, **7**, 2235.
64 E. T. Clarke, A. E. Martell and J. Reibenspies, *Inorg. Chim. Acta*, 1992, **196**, 177.
65 W. O. Nelson, S. J. Rettig and C. Orvig, *Inorg. Chem.*, 1989, **28**, 3153.
66 W. O. Nelson, T. B. Karpishin, S. J. Rettig and C. Orvig, *Inorg. Chem.*, 1988, **27**, 1045.
67 C. A. Matsuba, W. O. Nelson, S. J. Rettig and C. Orvig, *Inorg. Chem.*, 1988, **27**, 3935.

68 J. Burgess, J. Fawcett, M. A. Llewellyn, S. A. Parsons and D. R. Russell, *Transition Met. Chem. (Weinheim)*, 2000, **25**, 541.
69 P. S. Dobbin, R. C. Hider, A. D. Hall, P. D. Taylor, P. Sarpong, J. B. Porter, G. Xiao and D. van der Helm, *J. Med. Chem.*, 1993, **36**, 2448.
70 W. O. Nelson, S. J. Rettig and C. Orvig, *J. Am. Chem. Soc.*, 1987, **109**, 4121.
71 F. A. Cotton, G. Wilkinson, C. A. Murillo and M. Bochmann, *Advanced Inorganic Chemistry*, John Wiley & Sons, Inc., New York, 1999.
72 A. B. P. Lever, *Inorganic Electronic Spectroscopy*, Elsevier, Amsterdam, 1984.
73 S. M. Cohen, S. Petoud and K. N. Raymond, *Chem. Eur. J.*, 2001, **7**, 272.
74 G. Gran, *Analyst*, 1952, **77**, 661.
75 G. Choux and R. L. Benoit, *Bull. Soc. Chim. Fr.*, 1967, **8**, 2920.
76 R. Petrola, *Finn. Chem. Lett.*, 1985, 207.
77 E. T. Clarke and A. E. Martell, *Inorg. Chim. Acta*, 1992, **191**, 57.
78 E. T. Clarke and A. E. Martell, *Inorg. Chim. Acta*, 1992, **196**, 185.