Flavothionato metal complexes: implications for the use of hydroxyflavothiones as green pesticides†

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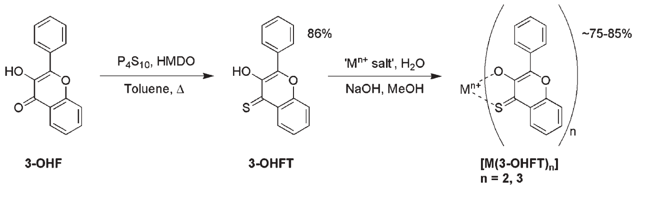
Transition-metal complexes of 3-hydroxyflavothiones have been prepared and structurally characterized; the photochemical properties of these complexes have been examined and are discussed in the context of the use of these compounds as photodegradable pesticides.

Flavones are a broad class of natural products that have been extensively studied for their antioxidant properties in the food and health sciences.[1] The photophysical properties of these organic chromophores have also been widely investigated, and flavones have even been utilized as fluorescent sensors.[2–4] The photochemical properties of sulfur-containing analogues, flavothiones, have also been studied in detail.[5–7] In particular, the photochemical behavior of 3-hydroxy substituted flavothiones has indicated that they might be promising candidates as environmentally friendly pesticides.[8] Studies with 3-hydroxyflavothione (3-OHFT) show that this compound can generate singlet oxygen and superoxide anions, and is effective at killing a variety of bacterial and fungal species.[8] The ability of 3-OHFT to photodegrade provides a mechanism by which the compound can be broken down and removed from the environment over time. Photodegradation of 3-OHFT has been extensively studied, showing that 3-OHFT photosensitizes oxygen to form singlet oxygen. The subsequent reaction of singlet oxygen with 3-OHFT is proposed to be the major degradative pathway.[9] Although the photodecomposition of 3-OHFT is too rapid for practical use, it holds promise as a lead compound for 'green pesticides.'[8]

Numerous studies are available on mixed O,S metal chelators, which have reported that these ligands avidly bind transition-metal ions.[10–15] In this context, the chemistry of 3-OHFT is intriguing as a potential thiopyrone metal chelator. It was anticipated that 3-OHFT would be a high affinity ligand for a variety of metal ions and that coordination to these ions would likely have an affect on the photochemical behavior of the ligand. Unexpectedly, no studies are available in the literature on this topic, which would likely be important if this or a related compound was utilized as a chemical pesticide where it would be exposed to an abundance of metal ions in an aerobic, terrestrial environment. Based on the aforementioned premise, this report describes the synthesis and photochemistry of transition-metal complexes of 3-OHFT. In addition, 3-OHFT and several metal complexes with this ligand have been structurally characterized by single crystal X-ray diffraction. As expected, we find that metal binding has a significant affect on the photodegradation of 3-OHFT.

Using a synthetic method similar to earlier reports,[5] 3-OHFT can be prepared in a single step and in good yield from 3-hydroxyflavone (3-OHF) as shown in Scheme 1.[12,16] The structure of 3-OHFT is consistent with other structures of thiopyrone compounds (Fig. S1).† [12] Combination of 3-OHFT with a variety of transition-metal salts in a mixed MeOH/water solution instantly formed coordination complexes that precipitated from solution and could be cleanly isolated by filtration in good yield (Scheme 1).† The structures of four transition-metal complexes with 3-OHFT have been determined (Fig. 1).‡ The structures of all four complexes, $[Co(3\text{-}OHFT)_3]$, $[Cu(3\text{-}OHFT)_2]$, $[Ni(3\text{-}OHFT)_2]$, and $[Zn(3\text{-}OHFT)_2]$ are similar to complexes with other O,S mixed ligands (Table S1).†[12,13] In general, 3-OHFT exhibits a strong *trans*-influence, resulting in a *cis* or *fac* coordination geometry;[12,13] however, $[Cu(3\text{-}OHFT)_2]$ displays a square planar geometry with a *trans*-geometry about the copper(II) ion.[17] This structure is somewhat surprising, but other copper(II) complexes with O,S mixed ligands have displayed the *trans* geometry,[13] contrary to the otherwise persistent *trans*-influence found with transition-metal complexes of O,S chelators similar to 3-OHFT.

In contrast to 3-OHFT, which has only weak emission upon UV irradiation,[5,6] several of the metal complexes were found to be fluorescent. To explore this effect, we examined the emission spectra of 3-OHFT upon addition of metal ions in methanol solution. A strong increase in fluorescence emission is observed in the presence of 1 equiv. of either zinc(II) or cadmium(II), with an approximately 15- and 17-fold increase at 520 and 530 nm, respectively (Fig. S2).† The $[Co(3\text{-}OHFT)_3]$ complex also showed an increase in emission relative to the free ligand. Emission enhancement upon binding of zinc(II) and cadmium(II) has been found in several fluorescent sensors designed to detect biologically available zinc(II).[18] Addition of iron(III), copper(II), or nickel(II) resulted in non-emissive, quenched species relative to the free ligand. The fluorescent properties of these compounds



Scheme 1 Synthesis of 3-OHFT and metal complexes.

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† Electronic supplementary information (ESI) available: Synthetic, spectroscopic, and crystallographic details, Table S1, and Fig. S1–S4. See DOI: 10.1039/b512185j

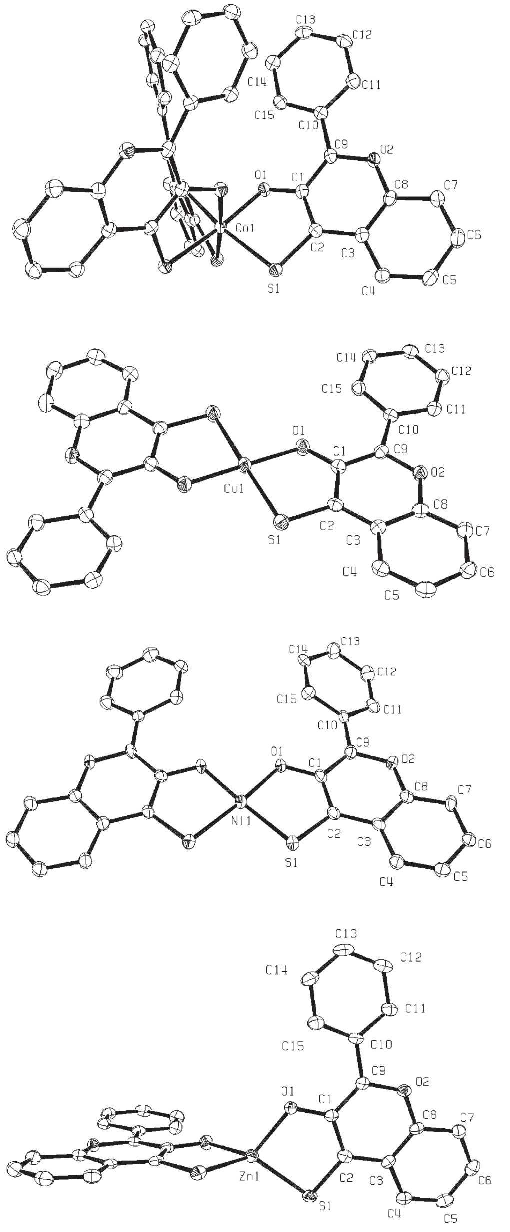

Fig. 1 Structural diagrams of (from top to bottom): [Co(3-OHFT)$_3$], [Cu(3-OHFT)$_2$], [Ni(3-OHFT)$_2$], and [Zn(3-OHFT)$_2$] with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms and solvent molecules have been omitted for clarity.

were essentially unchanged under either aerobic or anaerobic conditions.

Studies of 3-OHFT as a photodegradable pesticide found it to be among the most effective compounds from a variety of flavothiones examined. Unfortunately, the photodegradation of 3-OHFT was too rapid to be of practical use ($t_{1/2} \approx 3$ min under UVA lamp irradiation).[8] The pronounced effect of metal ions on the emissive properties of 3-OHFT suggested that metal complexation might also influence the photoreactivity of the ligand. Therefore, the photostabilities of 3-OHFT and several metal complexes were examined in chloroform solution by electronic spectroscopy upon exposure to ambient sunlight. Fig. 2 shows the change in electronic spectra for [Zn(3-OHFT)$_2$] during light exposure. The spectra clearly demonstrate that the zinc(II) complex completely decomposes within minutes ($t_{1/2} \approx 4$ min). In contrast, [Cu(3-OHFT)$_2$] remained stable over the same time period and was found to be stable after more than four days of natural light exposure (~12 h day^{-1}). The degradation of 3-OHFT and the metal complexes is light dependent, as control experiments performed in the dark showed no photodegradation over similar time durations (Fig. S3).† The degradation process is also facilitated by the presence of oxygen. For example, experiments with [Zn(3-OHFT)$_2$] under aerobic and anaerobic conditions, show that the decomposition process proceeds more rapidly in the presence of oxygen (Fig. S4).† Similar results were obtained with 3-OHFT and [Co(3-OHFT)$_3$], which is consistent with earlier findings that the major degradative pathway of 3-OHFT is mediated by singlet oxygen.[9]

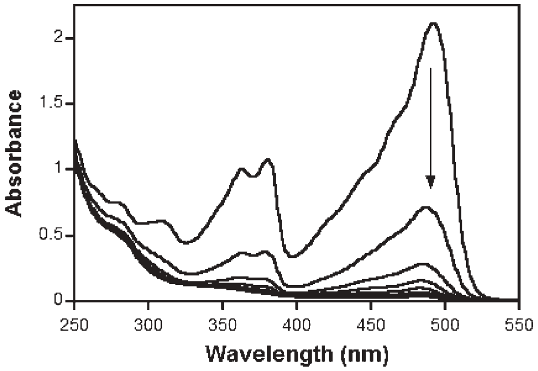

Fig. 2 UV-visible spectra of [Zn(3-OHFT)$_2$] in CHCl$_3$ (50 μM) under aerobic conditions in ambient sunlight monitored as a function of time. Eight spectra are shown at 5 min intervals from 0 to 35 min. The arrow highlights the rapid photodecomposition of [Zn(3-OHFT)$_2$] upon 0 to 5 min of exposure.

Interestingly, emissive metal complexes such as those with cobalt(III), zinc(II), and cadmium(II) decay at a comparable rate to free ligand ($t_{1/2}$ for 3-OHFT is $\leqslant 5$ min under the ambient light conditions used here). In contrast, metal ions that generate non-emissive complexes (iron(III), nickel(II), and copper(II)) significantly stabilize 3-OHFT against photodegradation. The decay profiles for several of the compounds, under aerobic conditions, are presented in Fig. 3. The stabilization trend observed is (from most to least stabilizing): $Cu^{2+} > Ni^{2+} > Fe^{3+} \gg$ 3-OHFT (free ligand) $\approx Co^{3+} \approx Zn^{2+} \approx Cd^{2+}$.

Based on these observations, the photostability of 3-OHFT can clearly be modulated by complexation to transition-metal ions. Metal ions that generate enhanced luminescence (cobalt(III), zinc(II), and cadmium(II)) result in fast photodecomposition. In contrast, photostability correlates well with metal ions that quench the excited state of the 3-OHFT ligand (iron(III), nickel(II), and copper(II)). From these data, several conclusions can be made about the mechanism of photostabilization by bound metal ions. First, the results strongly suggest that metal ions with unpaired electrons efficiently deactivate the $^3\pi, \pi^*$ excited state of 3-OHFT,[7,9] consistent with the observed quenching, thereby precluding the generation of singlet oxygen and protecting 3-OHFT from degradation. Quenching of organic excited states in the presence of, or upon binding to paramagnetic metal ions such as nickel(II) and copper(II) is a well established chemical

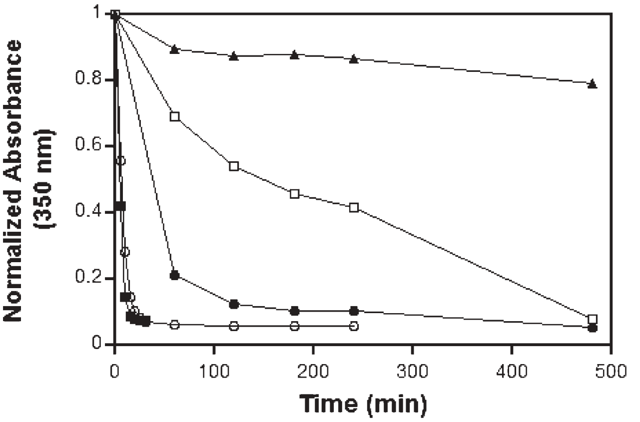

Fig. 3 Photodegradation of 3-OHFT (filled squares), [Co(3-OHFT)$_3$] (open circles), [Fe(3-OHFT)$_3$] (filled circles), [Ni(3-OHFT)$_2$] (open squares), and [Cu(3-OHFT)$_2$] (filled triangles) in $\mathrm{CHCl_3}$ (~50 μM) monitored by UV-visible absorption spectroscopy (350 nm).

phenomenon.[19] Second, the photodecomposition of the metal complexes does not appear to require pre-dissociation of the ligand (*i.e.* the observed photodegradation occurring only with transiently liberated 3-OHFT), as the kinetically inert cobalt(III) complex undergoes rapid photodegradation. Finally, the coordination geometry of the complex does not appear to be significant, as the tetrahedral [Zn(3-OHFT)$_2$] and octahedral [Co(3-OHFT)$_3$] both result in complexes that undergo swift photodegradation. Overall, paramagnetic ions that can deactivate the singlet oxygen-generating $^3\pi, \pi^*$ state of 3-OHFT effect photostabilization, while factors such as kinetic lability and coordination geometry do not contribute significantly to ligand photostabilty.

In summary, the first detailed characterization of flavothione metal complexes is reported. It is shown that the photochemical properties of 3-OHFT are substantially changed upon metal complexation. Emissive metal complexes are photodegraded rapidly upon exposure to sunlight. In contrast, binding to paramagnetic ions that quench the $^3\pi, \pi^*$ excited state of 3-OHFT, results in significant improvements in photostability, ranging from hours to days. The study of these complexes is important because of the potential use of 3-OHFT and other flavothiones as photodegradable pesticides. The limiting photodegradation of 3-OHFT might be alleviated if the compound was applied in the form of a metal complex that demonstrates a more suitable photodecay profile. Conversely, the persistence of these compounds in the environment may be unexpectedly extended by metal complexation upon exposure to metal ions in the earthly milieu. In either case, it is apparent that the metal complexation chemistry of these compounds must be considered when examining their use as potential green pesticides.

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Notes and references

‡ Crystal data for **[Co(3-OHFT)$_3$]**: Data were collected on a Bruker AXS diffractometer equipped with an area detector. $\mathrm{CoC_{45}H_{27}O_6S_3}$, $T = 100(2)$, rhombohedral, space group R-3, $a = 14.0289(7)$ Å, $b = 14.0289(7)$ Å, $c = 30.796(3)$ Å, $V = 5249.0(6)$ Å^3, $Z = 6$, final R indices [$I > 2\,\sigma I$]: $R_1 = 0.0428$, $wR_2 = 0.0884$, R indices (all data): $R_1 = 0.0616$, $wR_2 = 0.0946$. Crystal data for **[Cu(3-OHFT)$_2$]**: Data were collected on a Bruker AXS diffractometer equipped with an area detector. $\mathrm{CuC_{30}H_{18}O_4S_2}$, $T = 100(2)$, monoclinic, space group $P2_1/n$, $a = 13.6476(17)$ Å, $b = 9.8509(12)$ Å, $c = 17.256(2)$ Å, $\beta = 92.0970(10)$, $V = 2318.3(5)$ Å^3, $Z = 4$, final R indices [$I > 2\,\sigma I$]: $R_1 = 0.0381$, $wR_2 = 0.0908$, R indices (all data): $R_1 = 0.0588$, $wR_2 = 0.1001$. Crystal data for **[Ni(3-OHFT)$_2$]**: Data were collected on a Bruker AXS diffractometer equipped with an area detector. $\mathrm{NiC_{31}H_{19}O_4S_2Cl_3}$, $T = 273(2)$, monoclinic, space group $P2_1/n$, $a = 7.6947(18)$ Å, $b = 39.596(9)$ Å, $c = 9.965(2)$ Å, $\beta = 112.643(3)^\circ$, $V = 2801.9(11)$ Å^3, $Z = 4$, final R indices [$I > 2\,\sigma I$]: $R1 = 0.0841$, $wR_2 = 0.1955$, R indices (all data): $R_1 = 0.0951$, $wR_2 = 0.2041$. Crystal data for **[Zn(3-OHFT)$_2$]**: Data were collected on a Bruker AXS diffractometer equipped with an area detector. $\mathrm{ZnC_{31}H_{20}O_4S_2Cl_2}$, $T = 100(2)$, triclinic, space group P-1, $a = 9.6538(5)$ Å, $b = 10.6359(6)$ Å, $c = 13.9037(8)$ Å, $\alpha = 92.0790(10)^\circ$, $\beta = 98.5820(10)^\circ$, $\gamma = 105.6480(10)^\circ$, $V = 1354.89(13)$ Å^3, $Z = 2$, final R indices [$I > 2\,\sigma I$]: $R_1 = 0.0691$, $wR_2 = 0.1393$, R indices (all data): $R_1 = 0.0764$, $wR_2 = 0.1423$. CCDC 25675–282323. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b512185j

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