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## COMMUNICATION

## Photochemically-induced dioxygenase-type CO-release reactivity of group 12 metal flavonolate complexes<sup>†</sup>

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Exposure of 3-hydroxyflavonolate complexes of the group 12 metals to UV light under aerobic conditions results in oxidative carbon-carbon bond cleavage and CO release. This reactivity is novel in that it occurs under mild reaction conditions and suggests that light-induced CO-release reactivity involving metal flavonolate species may be possible in biological systems.

Flavonoids are a class of a naturally occurring, polyphenolic substances produced in plants. They are of current interest as potential therapeutic agents due to their anti-microbial, anti-oxidative, and UV-protective activity.<sup>1</sup> A prominent member of this family of compounds is quercetin (Fig. 1), a natural compound that is being investigated to prevent or treat a variety of diseases.<sup>1a,2</sup> Quercetin is found in an assortment of foods including black and green tea, red onions, and many other fruits and vegetables that are widely touted for their beneficial health effects.

Studies of the interactions of flavonoids with metal ions are essential toward understanding how complexation modulates the reactivity properties of the flavonoid.<sup>3</sup> Investigations of metalflavonoid species are also relevant toward understanding the active site chemistry of quercetinases from fungi and bacteria that catalyze oxidative cleavage of the C(2)–C(3) bond (a dioxygenasetype reaction; Fig. 1) and CO release.<sup>4,5</sup> In another area of research, metal complexes of 3-hydroxyflavonol (3-Hfl, Fig. 1 (bottom)) are being used as model systems to evaluate intereactions between components of soil organic matter and bioavailable or contaminating heavy metal ions.<sup>6</sup> To adequately address these areas, systematic studies of structure/reactivity relationships of metal flavonolate complexes are needed, including studies involving environmentally toxic metals ions such as Cd( $\Pi$ ) and Hg( $\Pi$ ). However, to date, such systematic studies are lacking, and while the chemistry of copper flavonolate species has been significantly advanced in recent years,<sup>7</sup> far fewer X-ray crystallographically characterized flavonolate complexes of other metal ions have been reported.<sup>8</sup> To address this deficiency, we recently prepared and characterized the first series of 3-Hfl complexes of the 3*d* metals, including a Zn(II) derivative, [(6-Ph<sub>2</sub>TPA)Zn(3-Hfl)]ClO<sub>4</sub> (1; 6-Ph<sub>2</sub>TPA, *N*,*N*-bis((6-phenyl-2-pyridyl)methyl)-*N*-((2-pyridyl)methyl)amine).<sup>9</sup>

Outlined herein is the first systematic study of the structural, spectroscopic, and aerobic photochemical reactivity properties of group 12 metal 3-Hfl complexes. Our results demonstrate that all three group 12 metal ions form isolable flavonolate complexes that can be characterized by X-ray crystallography, and that each complex undergoes an aerobic photochemically-induced dioxygenase-type reaction to release CO and form a metal-depside complex. These results are novel for a number of reasons. First, aerobic *photoinduced* flavonoid ring-opening and CO release under mild conditions has not been previously reported for any metal flavonolate complex. Second, the observed dioxygenase reactivity for the complexes contrasts with prior reports of Zn(II)-flavonolate species that exhibit photoisomerization reactivity akin to that found for free 3-hydroxyflavonol.<sup>10</sup>

The Cd(II) and Hg(II) flavonolate complexes [(6-Ph<sub>2</sub>TPA)-M(3-Hfl)]ClO<sub>4</sub> (M = Cd(II), **2**; M = Hg(II), **3**) were prepared



**Fig. 1** Top: Structure of quercetin (including numbering of C–C bond that undergoes oxidative cleavage) and the reaction catalyzed by quercetinase enzymes. Bottom: Structure of 3-hydroxyflavonol (3-Hfl) and labelling of rings.

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<sup>&</sup>lt;sup>†</sup> Electronic supplementary information (ESI) available: Details of experimental procedures including synthetic and characterization data for **2**, **3**, and **4–6**; <sup>18</sup>O<sub>2</sub> labeling experiments for the reactions of **1** and **2**. CCDC 832449–832452. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc13961d



**Fig. 2** Thermal ellipsoid drawings of the cationic portions of **2** and **3**. Ellipsoids are plotted at the 50% probability level. Hydrogen atoms are omitted for clarity.

in a similar manner to the Zn(II) analog.<sup>9</sup> Each complex was characterized by X-ray crystallography, elemental analysis, IR, multinuclear NMR, UV-vis, and fluorescence. While the Zn(II) center of 1 has a coordination number of five in the solid state, the Cd(II) and Hg(II) analogs 2 and 3 exhibit a distorted octahedral geometry (Fig. 2).<sup>11</sup> In both complexes the ketone oxygen of the C ring is coordinated *trans* to the tertiary amine nitrogen of the chelate ligand. The average M-O distance involving the flavonolate oxygen atoms increases down the group (1: 2.03 Å; 2: 2.25 Å; 3: 2.30 Å),<sup>12</sup> and the asymmetry of the flavonolate coordination  $(\Delta_{M-\Omega})$  is largest for the Zn(II) and Hg(II) derivatives (0.17 and 0.21 Å, respectively). The flavonolate moiety in 2 and 3 is positioned between the phenyl appendages of the 6-Ph<sub>2</sub>TPA ligand (Fig. 2). The average distance between the centroid of ring C of the flavonolate and the centroids of the aryl rings of the chelate ligand is  $\sim 4.0$  Å.

Comparison of the <sup>1</sup>H NMR spectra of 1-3 (Fig. S1, Supporting Information<sup>†</sup>) shows that each complex has effective  $C_{\rm s}$  symmetry in solution with equivalent phenyl-appended pyridyl appendages. There are interesting differences in the <sup>1</sup>H NMR spectra of this series of complexes in terms of the chemical shifts of proton resonances associated with the phenyl appendages of the 6-Ph<sub>2</sub>TPA ligand. Namely, in 2 and 3 the resonances of the *meta* and *para* protons of the phenyl appendages are shifted upfield, which is consistent with  $\pi$ -stacking involving the C ring of the flavonolate. Additionally, the signal for the C(1)-H of the unsubstituted pyridyl ring in 2 and 3 is shifted downfield by  $\sim 0.9$  ppm relative to the same signal in 1. We attribute this deshielding to the presence of close contact between C(1)-H of the unsubstituted pyridyl ring and the carbonyl O(2) atom of the coordinated flavonolate (for both complexes 2 and 3 the C(1)  $\cdot \cdot \cdot$  O(2) distance is ~ 3.0 Å).

The band I transition of the flavonolate moiety of **2** is found at 430 nm and is red-shifted relative to that of **1** (420 nm) and **3** (415 nm). Fluorescence emission spectra of the complexes show a Stokes shift of 60 nm for **1** and **3**, and 46 nm for **2** (Fig. S2–S4, Supporting Information†). The excited states associated with these emissions have lifetimes of ~2.0 ns (**1**: 2.0(1) ns; **2**: 1.7(1) ns; **3**: 2.0(1) ns). The fluorescence quantum yields for **1**–**3** are 0.18, 0.06, and 0.02, respectively. We note that the complexes presented herein have lower fluorescence quantum yields than that previously reported for  $[Zn(3-Hfl)]^+$  (0.38), albeit the structure of this species has not been determined.<sup>10</sup>

The divalent metal flavonolate complexes 1-3 are stable with respect to exposure to oxygen in the solid state under room light for >90 days. However, exposure of aerobic CH<sub>3</sub>CN solutions of **1–3** to UV light (Rayonet, 300 nm irradiation) at ambient temperature results in high-yield dioxygenase-type reactivity to give the depside complexes [(6-Ph<sub>2</sub>TPA)M(*O*-bs)]-ClO<sub>4</sub> (M = Zn (4), Cd (5), Hg (6); *O*-bs = *O*-benzoylsalicylate) and CO.<sup>13</sup> Each reaction proceeds with a high quantum yield at 300 nm: **1** ( $\Phi$  = 0.9), **2** ( $\Phi$  = 1.0), and **3** ( $\Phi$  = 0.8). The lower reaction quantum yield of the Hg(II) complex is due to enhanced spin–orbit coupling.<sup>14</sup> Use of <sup>18</sup>O<sub>2</sub> in the reactions of **1** and **2** resulted in quantitative incorporation (>98% as determined by mass spectrometry and FTIR) of two labeled oxygen atoms into the depside ligand. Comparison of the fully assigned <sup>13</sup>C NMR spectra of **2**, **5** and [(6-Ph<sub>2</sub>TPA)Cd(CH<sub>3</sub>CN)](ClO<sub>4</sub>)<sub>2</sub> (7, Fig. S5–S7; Supporting Information<sup>‡</sup>) clearly show that the carbon lost as CO is derived from the C(31)–O(1) unit (Fig. 2).

Complexes 4 and 5 were characterized by X-ray crystallography, elemental analysis, NMR and IR spectroscopy, and mass spectrometry. Complex 6 was characterized by NMR and IR spectroscopy, and mass spectrometry. The cationic portions of 4 and 5 are shown in Fig. 3. In  $4^{15}$  the zinc center has a nearly trigonal bipyramidal geometry,<sup>16</sup> with the *O*-bs ligand coordinated in a monodentate fashion in an axial position.<sup>17</sup> In 5, the depside is coordinated as a bidentate ligand.<sup>17,18</sup> The spectroscopic properties of the depside complexes 4 and 5 are as expected (Fig. S8). We note that <sup>1</sup>H NMR spectra of 6 give evidence for a small amount of loss of the 6-Ph<sub>2</sub>TPA ligand in CD<sub>3</sub>CN solutions of this complex.<sup>19</sup>

The results presented herein are novel when considered in the context of the previously reported photochemistry of 3-Hfl. Irradiation of a pyridine solution of 3-Hfl using a 300 W tungsten lamp, in the presence of a photosensitizer (bengal rose), has been reported to result in the formation of the photooxygenation products depside (*O-bs*) and CO.<sup>20</sup> This reaction involves the generation of <sup>1</sup>O<sub>2</sub> which reacts with ground state 3-Hfl. Studer, *et al.* reported that photooxygenation of 3-Hfl occurs in O<sub>2</sub>-saturated nonpolar solvents in the absence of a photosensitizer.<sup>21</sup> In this case, photooxygenation



Fig. 3 Thermal ellipsoid drawings of the cationic portions of 4 and 5. Ellipsoids are plotted at the 50% probability level. Hydrogen atoms are omitted for clarity.

was suggested to result from reaction between a triplet tautomer state, wherein the C(3) hydroxyl proton has been transferred to the C(4)-carbonyl moiety in a zwitterionic structure, and ground state  ${}^{3}O_{2}$ . We note that this chemistry is solvent dependent, as in CH<sub>3</sub>OH, CH<sub>3</sub>CN, or CH<sub>2</sub>Cl<sub>2</sub>, photooxygenation does not happen and instead photorearrangement to give 3-phenyl-3-hydroxy-1,2-inandione occurs.<sup>22,23</sup>

Previously, the presence of metal ions was reported to prevent the photoinduced rearrangment of neutral 3-Hfl, or have no effect on the photochemical reaction.<sup>10,23*a*</sup> However, the results presented herein show that metal 3-hydroxyflavonolate complexes can undergo photoinduced dioxygenase-type CO-release reactivity when irradiated with UV light. In these complexes the coordinated flavonolate anion is akin to the tautomeric structure of 3-Hfl,<sup>21</sup> thereby enabling photo-induced photooxygenation and CO-release reactivity. Notably this reactivity occurs under conditions that are considerably milder than those reported for thermal dioxygenase-type reactions of Cu(3-Hfl) complexes.<sup>7</sup> Overall, the results presented herein suggest that the formation of metal-flavonolate species in nature may enable light-induced dioxgyenase-type CO-release reactivity under mild conditions.

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- 18 5: C<sub>46</sub>H<sub>38</sub>CdClN<sub>5</sub>O<sub>8</sub>, M = 936.66, triclinic, a = 14.2066(2), b = 13.24300(10), c = 14.3060(2) Å, U = 2075.18(5) Å<sup>3</sup>, T = 151(1)K, space group  $P\bar{1}$ , Z = 4, 17877 reflections measured, 9483 unique ( $R_{\text{int}} = 0.0202$ ) which were used in all calculations. The final R values ( $I > 2\sigma(I)$ ) are  $R_1 = 0.0348$  and w $R_2 = 0.0749$ .
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