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## COMMUNICATION

## Side-on Cupric-Superoxo triplet complexes as competent agents for H-abstraction relevant to the active site of PHM

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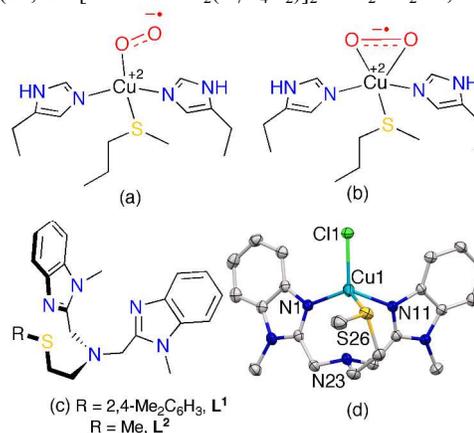
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**Copper complexes with N<sub>3</sub>S donors inspired on the Cu<sub>M</sub> site of copper monooxygenases react with O<sub>2</sub> affording side-on cupric-superoxo complexes capable of H-abstraction from dihydroanthracene and THF. Spectroscopic and DFT data of the Cu-superoxo support a spin triplet ground state for the side-on complexes, as well as a hemilabile thioether.**

Dioxygen activation by earth-abundant copper in chemical and biochemical systems is an intense area of research due to its relevance in the functionalisation of a wide range of substrates:<sup>1</sup> understanding the intimate details of O<sub>2</sub> activation at copper centres may lead to the efficient use of dioxygen in selective oxidative transformations. In copper enzymes, the readily accessible Cu<sup>2+</sup>/Cu<sup>+</sup> redox couple is involved in the selective oxidation of hydrocarbons,<sup>1d</sup> including the hydroxylation of methane.<sup>2</sup> Intriguingly, some of the active sites of copper monooxygenases that activate strong aliphatic C-H bonds<sup>3</sup> feature methionine-derived sulfur donors in addition to the ubiquitous imidazole donors from histidine residues (His<sub>2</sub>Met). These thioether donors present in the Cu<sub>M</sub> sites of peptidylglycine  $\alpha$ -hydroxylating monooxygenase (PHM), dopamine  $\beta$ -monooxygenase (D $\beta$ M), and tyramine  $\beta$ -monooxygenase (T $\beta$ M)<sup>4</sup> appear to modulate the redox potential of the Cu<sup>2+</sup>/Cu<sup>+</sup> couple. Nonetheless, a detailed understanding of the electronic influence of thioethers to selectively hydroxylate unactivated C-H bonds remains elusive. An additional question that arises in these systems is the inertness of the thioether moiety towards oxidation during catalytic turnover conditions that could potentially result in the corresponding sulfoxide or sulfone.

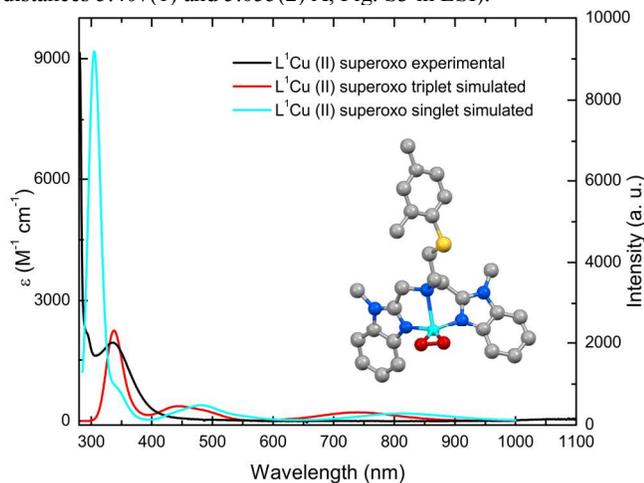
A precatalytic end-on cupric superoxo complex [Cu<sub>M</sub><sup>2+</sup>- $\eta^1$ -O<sub>2</sub><sup>-</sup>] has been established by X-ray crystallography (Scheme 1a),<sup>3a</sup> although side-on  $\eta^2$ -O<sub>2</sub>-bound complexes have also been evaluated as viable intermediates responsible for C-H activation (Scheme 1b).<sup>5</sup> Model complexes have been designed based on the His<sub>2</sub>Met active sites of Cu-monooxygenases to gain insight on the properties of [Cu-O<sub>2</sub>] adducts, particularly cupric superoxos. Efforts have focused on tripodal ligands with tetradentate N<sub>3</sub>S donor sets,<sup>6</sup> including a recent

report on a pyridine-supported, thioether-containing [Cu<sup>2+</sup>- $\eta^1$ -O<sub>2</sub><sup>-</sup>] complex.<sup>6d</sup> Benzimidazole-based N<sub>3</sub>S-copper complexes mimic specific aspects of monooxygenase enzymes: oxygenation of [L<sup>1</sup>Cu]ClO<sub>4</sub> resulted in electrocatalytic O<sub>2</sub><sup>-</sup> formation, presumably via a putative Cu<sup>2+</sup>-superoxo.<sup>7</sup> This reactivity is related to the strong  $\sigma$ -donor properties of benzimidazoles, which place them as closer analogues of histidine than pyridine and amine derivatives, based on the p*K*<sub>a</sub> and *K*<sub>ass</sub> with Cu<sup>2+</sup>.<sup>7a,8</sup> To further establish the capability of benzimidazole-based platforms to emulate histidine donors in copper monooxygenases, we herein report a detailed study of the reactivity of O<sub>2</sub> with [L<sup>1</sup>Cu]<sup>+</sup> and the related [L<sup>2</sup>Cu]<sup>+</sup>, featuring a methylthioether group to more closely approach the histidine donor in PHM (L<sup>1</sup>, L<sup>2</sup>: [N-Me-2-CH<sub>2</sub>(C<sub>7</sub>H<sub>4</sub>N<sub>2</sub>)<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>SR, Scheme 1c).



**Scheme 1** (a) Precatalytic end-on Cu-superoxo [Cu<sup>2+</sup>- $\eta^1$ -O<sub>2</sub><sup>-</sup>] in PHM; (b) side-on Cu-superoxo [Cu<sup>2+</sup>- $\eta^2$ -O<sub>2</sub><sup>-</sup>] analogue; (c) ligands employed; (d) Mercury diagram of L<sup>2</sup>CuCl at the 50% probability level; H-atoms omitted for clarity. Selected bond distances (Å): Cu1-N1 2.053(2), Cu1-N11 2.027(2), Cu1-S26 2.691(1), Cu1-Cl1 2.350(1); angles (°): N1-Cu1-N11 116.35(7), N1-Cu1-S26 123.65(5), N11-Cu1-S26 86.86(5), N1-Cu1-Cl1 112.47(5), N11-Cu1-Cl1 114.36(5), S26-Cu1-Cl1 100.29(2).

Comparison of the coordination environment provided by  $L^2$  with the His<sub>2</sub>Met donor set in PHM was allowed by the solid-state structure of  $L^2CuCl$  (and its  $Cu^{2+}$  analogue, Fig. S2 in ESI†). The complexes were obtained from the reaction of equimolar amounts of  $L^2$  and the appropriate copper salt. The  $Cu^+$  centre in  $L^2CuCl$  is in a distorted tetrahedral environment defined by benzimidazole N, thioether S, and Cl atoms, with the tertiary amine at a non-bonding distance of 2.819(2) Å (Scheme 1d). The average Cu-N bond length of 2.04 and Cu-S distance of 2.691(1) Å are comparable to the corresponding Cu-N and Cu-S distances of 2.03 and 2.68 Å in PHM.<sup>9</sup> Both  $L^1$  and  $L^2$  give rise to thioether-bridged  $Cu^+$  dimers in the solid state when non-coordinating counterions are employed ( $[L^aCu]_2X_2$ ,  $X^- = ClO_4^-$ ,<sup>7a</sup>  $CF_3SO_3^-$  (OTf));  $Cu \cdots Cu$  distances 5.407(1) and 5.055(2) Å, Fig. S3 in ESI).



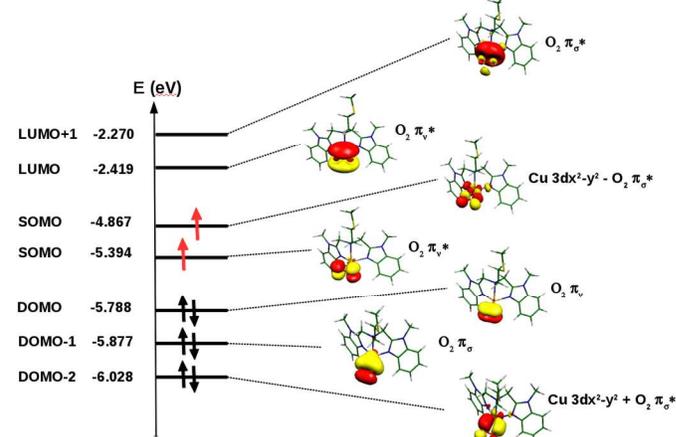
**Fig. 1** Experimental UV-vis spectrum of  $[L^1Cu]^+$  after bubbling  $O_2$  in THF at  $-80^\circ C$  (intensity in  $\epsilon$ ), and simulated spectra for triplet and singlet S-uncoordinated side-on optimised  $[L^1Cu-\eta^2-O_2]^+$  (intensity in a.u.). Inset: optimised structure of the triplet.

$[L^aCu]_2OTf_2$  are nonetheless monomeric in THF solution, as corroborated by  $^1H$  NMR spectroscopy: both complexes give rise to a single set of relatively sharp resonances for the equivalent benzimidazole groups in THF- $d_8$ , even at  $-40^\circ C$  (Fig. S5), consistent with monomeric  $[L^aCu]^+$  formulations. The presence of aggregates would likely result in more than the two multiplets observed for the  $NCH_2CH_2S$  linkers between  $\delta$  3.3–3.5 ppm.<sup>10d</sup> Furthermore, DOSY NMR confirmed the monomeric nature of the complexes (Fig. S6).

Bubbling  $O_2$  into THF solutions of  $[L^aCu]^+$  at  $-80^\circ C$  resulted in ESR-silent species after 15 min, with very similar optical features for both  $L^1$  and  $L^2$ -complexes that are stable for at least 2 h ( $L^1$ :  $\lambda = 336, 614$  nm,  $\epsilon \sim 1500, 285 M^{-1}cm^{-1}$ ;  $L^2$ :  $\lambda = 339, 609$  nm,  $\epsilon \sim 2300, 119 M^{-1}cm^{-1}$ , Figs. 1 and S12). High energy charge transfer bands have been associated to dimeric side-on bridging peroxo complexes  $[Cu^{2+}_2-\mu-\eta^2:\eta^2-O_2]$  with extinction coefficients  $> 20,000 M^{-1}cm^{-1}$ .<sup>11,12</sup> Although incomplete oxygenation could account for the low apparent  $\epsilon$  values, addition of chelating anions such as  $PhCO_2^-$  or  $CH_3SO_3^-$  that favour the formation of side-on peroxo dimers did not have an effect on  $O_2$ -saturated solutions of  $[L^aCu]^+$  (Figs. S15 and S16).<sup>13,14</sup> A better fit of the observed optical features corresponds to side-on cupric-superoxo species  $[Cu^{2+}-\eta^2-O_2^-]$  that lack thioether bonding, similar to those reported by Tolman and coworkers (see DFT studies below).<sup>10</sup> Confirmation of the proposed mononuclear  $[L^aCu^{2+}-\eta^2-O_2^-]$  formulations by resonance Raman spectroscopy was likely precluded by the photosensitivity of frozen solutions (liquid  $N_2$ ,  $\lambda_{ex}$  335 nm) at  $-125$  or  $-80^\circ C$  in 2-MeTHF or THF, respectively. Nonetheless, the reaction of  $[L^1Cu]OTf$  with  $O_2$

in THF- $d_8$  at  $-80^\circ C$  was monitored by  $^1H$  NMR ( $[L^2Cu]OTf$  is considerably less soluble at this temperature). The spectrum in Fig. S12 reveals a single set of paramagnetically broadened signals reminiscent of the ESR-silent  $[Cu(HIPT_3tren)O_2]^+$  reported by the group of Itoh,<sup>15</sup> and assigned as a spin triplet by Karlin, Solomon, and coworkers.<sup>16</sup> Signal broadening by thioether-bridged dimer formation appears to be restricted to  $Cu^+$  complexes.<sup>10d</sup>

To gain insight on the bonding and electronic properties of  $[L^aCuO_2]^+$ , DFT studies were carried out with the ORCA software package.<sup>17</sup> Di- and monocopper species, with and without S-bonding ( $N_3S$  vs  $N_3$  donor sets) were considered in both singlet and triplet states. Experimental data were confronted with theoretical calculations by comparing UV-vis spectra with TD-DFT results. Geometry optimisation of side-on bridging peroxos  $[Cu^{2+}_2-\mu-\eta^2:\eta^2-O_2]$  resulted in S-uncoordinated ( $N_3$ ) singlet species that give rise to UV-vis spectra drastically different from the experimental ones (Figs. S17, S18), with very intense bands predicted at ca. 410 and 550 nm for  $L^1$ , and 370 and 450 nm for  $L^2$  complexes, respectively (Figs. S19, S20). Optimisation of monomeric thioether-bonded complexes ( $N_3S$ ) resulted in triplet end-on cupric-superoxos (Figs. S21, S22), the singlets being higher in energy by 17 kJ/mol as expected.<sup>16</sup> The TD-DFT calculated data for the triplet end-on  $[L^aCuO_2]^+$  species differ considerably from the experimental UV-vis spectra, with absorbances at ca. 400 and 550 nm for  $[L^1CuO_2]^+$ , and 475 nm for  $[L^2CuO_2]^+$  (Fig. S23). Monomeric complexes with uncoordinated thioethers result in side-on structures that were analysed as singlets and triplets (Figs. 1, S24, S25). A better match of electronic spectra is obtained for the triplet states with respect to the experimental ones, with a strong band predicted around 340 nm, and a  $d-d$  band at ca. 740 nm (Fig. 1, red trace, and Fig. S26); in contrast, the calculated UV-vis spectra of the singlets predict intense transitions around 300 nm (Fig. 1, blue trace). For  $[L^1CuO_2]^+$  an exchange coupling constant  $J = +250 cm^{-1}$  (spatial overlap  $S = 0.568$ ) was obtained from BS-DFT calculations (Fig. S29). This value shows that the two unpaired electrons of the complex are strongly ferromagnetically coupled, consistent with a triplet ground spin state that is stabilised by 6.0 kJ/mol with respect to the singlet. Similar results were obtained for  $[L^2CuO_2]^+$  with a calculated exchange coupling constant of  $+237 cm^{-1}$  (spatial overlap  $S = 0.570$ ) consistent with a strong ferromagnetic interaction. The triplet is also the favoured ground spin state by 5.7 kJ/mol (Fig. S30, Table S4).



**Fig. 2** Molecular orbital diagram of triplet side-on superoxo  $[L^2CuO_2]^+$  with uncoordinated methylthioether.

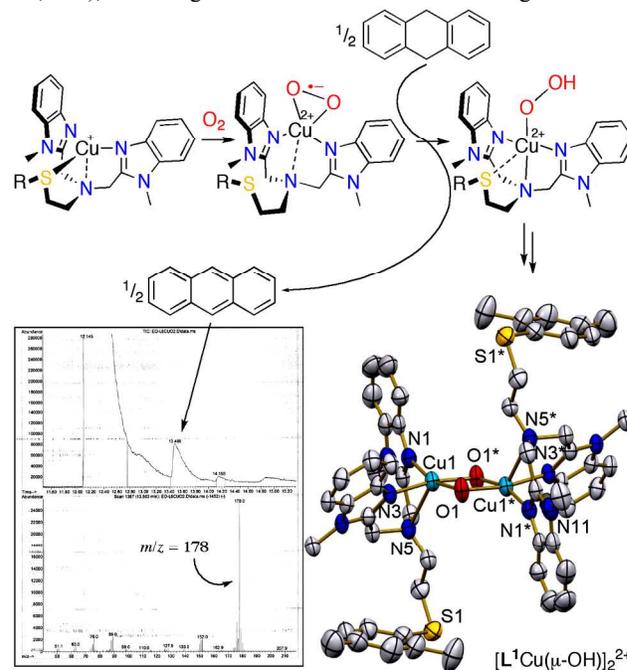
For both side-on  $[L^aCuO_2]^+$  complexes a ferromagnetic interaction is expected from an MO analysis due to the orthogonality of the two magnetic orbitals depicted in Figs. S31 and S32. The first one is an almost pure superoxide-centred  $\pi^*_v$  orbital perpendicular to

the Cu–OO plane, while the second one corresponds to the antibonding interaction of Cu  $dx^2-y^2$  and the  $\pi^*_\sigma$  orbital (Figs. 2, S33, S34). Although side-on coordination of superoxide anion to  $\text{Cu}^{2+}$  centres has been associated with singlet ground states,<sup>16</sup> it is noteworthy in the case of  $[\text{L}^n\text{CuO}_2]^+$  that the long calculated Cu–O distances of 1.97 Å imply a relatively weak bond (experimental av. Cu–O distance for side-on cupric-superoxo complexes 1.84 Å).<sup>10,18</sup> Consequently, the bonding/antibonding interaction between the Cu  $dx^2-y^2$  orbitals and the superoxo  $\pi^*_\sigma$  orbitals in  $[\text{L}^n\text{CuO}_2]^+$  is weaker than the spin-pairing energy (likely intermediate in magnitude between canonical side-on and end-on Cu–O<sub>2</sub> interactions previously described),<sup>16</sup> resulting in a triplet ground state. The geometry around the  $\text{Cu}^{2+}$  centres is square pyramidal, with the O and N-atoms from benzimidazole donors in the basal positions (Cu–N average distance 1.96 Å), and the tertiary amine in the apical positions at a considerably longer distance (2.38 Å), defining N<sub>3</sub> donor sets from  $\text{L}^n$  (calculated Cu⋯S distances 5.86 and 5.83 Å, respectively). The weak Cu–O interactions predicted for  $[\text{L}^n\text{CuO}_2]^+$  may be ascribed to the strongly  $\sigma$ -donating benzimidazoles, consistent with Natural Bond Order (NBO) analysis. The calculated Wiberg index for the Cu–N bonds is indeed larger (0.83) than that for the Cu–O bonds (0.73).<sup>19</sup> As a consequence, the superoxo moieties in the optimised square pyramidal triplet complexes bear a considerable amount of spin density, which may predispose them for H-abstraction.

In this context, attempts to isolate  $[\text{L}^n\text{CuO}_2]\text{OTf}$  from reactions of  $[\text{L}^n\text{Cu}]\text{OTf}$  and  $\text{O}_2$  in THF at  $-78^\circ\text{C}$  resulted in the commonly observed bridging hydroxo complexes, evidencing solvent C–H activation by the triplet side-on superoxos. Blue crystals of  $[\text{L}^1\text{Cu}(\mu\text{-OH})_2]\text{OTf}_2$  were obtained after a week, with symmetry-related  $\text{Cu}^{2+}$  centres in square pyramidal N<sub>3</sub>O<sub>2</sub> coordination environments (Cu⋯S distance 6.01 Å, Fig. 3). The dimers are insoluble in THF at  $-80^\circ\text{C}$ , with solid-state UV-vis spectra distinct from those of  $[\text{L}^n\text{CuO}_2]^+$ , lacking the intense absorption at  $\sim 340$  nm, Fig. S42. H-abstraction from THF by  $[\text{L}^2\text{CuO}_2]^+$  was confirmed by UV-vis spectroscopy at  $-40^\circ\text{C}$  ( $k = 1.78 \times 10^{-4} \text{ s}^{-1}$ ;  $t_{1/2} = 3894$  s, Figs. S44, S45). The capability for C–H activation was further evaluated with 9,10-dihydroanthracene (DHA) as H-donor. The intensity of the charge transfer band at  $\sim 340$  nm diminished over an hour with pseudo first-order behaviour upon addition of a 10-fold molar excess (3 mM solution of DHA in THF) to 0.3 mM solutions of  $[\text{L}^n\text{CuO}_2]^+$  at  $-60^\circ\text{C}$  (for  $\text{L}^2$ ,  $k = 0.002 \text{ s}^{-1}$ ;  $t_{1/2} = 315$  s, Figs. S45, S46). Dilution of the samples with 3 mL of  $\text{CH}_2\text{Cl}_2$ , followed by quenching with 0.5 M aqueous  $\text{Na}_2\text{EDTA}$ , evidenced the presence of anthracene and anthraquinone as oxidation products. In the case of  $[\text{L}^1\text{CuO}_2]^+$  the products were obtained in 1:1 ratio. Significantly,  $[\text{L}^2\text{CuO}_2]^+$  is more selective for H-abstraction without further oxidation, affording the products in 7:3 ratio (by GC-MS, Figs. 3, S48, S49). Similar H-abstraction and further oxidation of DHA has been observed with  $[\text{Cu}^{2+}_2-\mu-\eta^2-\eta^2-\text{O}_2]$  and  $[\text{Cu}^{3+}_2(\mu\text{-O})_2]$  species, albeit with longer reaction times,<sup>11b</sup> predominant formation of anthraquinone,<sup>20</sup> or requiring a larger excess of DHA.<sup>21</sup> Among cupric-superoxo complexes, singlet side-on species do not react with C–H bonds.<sup>10,18</sup> Triplet end-on superoxos perform H-abstraction, provided that the  $\text{Cu}^{2+}$  centres are in a tetragonal environment,<sup>6d,22</sup> trigonal bipyramidal (TBP) complexes being less reactive.<sup>23</sup> This behaviour parallels the reactivity of tetragonal cupric-hydroperoxo complexes that activate C–H bonds,<sup>24</sup> compared to their relatively unreactive TBP counterparts.<sup>25</sup> Within this context, triplet side-on complexes  $[\text{L}^n\text{CuO}_2]^+$  fulfill the requirements for enhanced H-abstraction ability: tetragonal geometry and a triplet ground state.

Since charge-transfer bands have been described for  $\text{Cu}^{2+}$ -hydroperoxo complexes around 360 nm,<sup>6a,24,25a</sup> which may form by rapid H-abstraction from solvent, we ruled out such  $[\text{L}^n\text{Cu-OOH}]^+$  species as the observed oxygenation products of  $[\text{L}^n\text{Cu}]^+$ .  $\text{Cu}^{2+}$ -

hydroperoxides were prepared by addition of 5–10 equivs of 1:1  $\text{H}_2\text{O}_2/\text{Et}_3\text{N}$  THF solutions to the appropriate  $[\text{L}^n\text{Cu}]^{2+}$  sources. In addition to being relatively stable at room temperature and ESR-active, the electronic spectra are distinct from those of  $[\text{L}^n\text{CuO}_2]^+$  (Figs. S35–S42), with shoulders around 330 and 310 nm potentially due to  $\text{S} \rightarrow \text{Cu}^{2+}$  charge-transfer bands of thioether-bound cupric-hydroperoxos.<sup>6a,7</sup> Addition of DHA to solutions of  $[\text{L}^n\text{Cu-OOH}]^+$  at  $20\text{--}40^\circ\text{C}$  resulted in only trace amounts of oxidation products (Figs. S50, S51), excluding them as efficient H-abstraction agents.



**Fig. 3** Proposed reaction of  $[\text{L}^1\text{CuO}_2]^+$  with DHA affording the final products anthracene and  $[\text{L}^1\text{Cu}(\mu\text{-OH})_2]^{2+}$ ; Mercury diagram of  $[\text{L}^1\text{Cu}(\mu\text{-OH})_2]^{2+}$  at the 50% probability level. Selected bond distances (Å): Cu1–O1 1.913(2), Cu1–O1\* 1.917(3), Cu1–N1 2.006(3), Cu1–N3 1.985(2), Cu1–N5 2.460(3); angles ( $^\circ$ ): N1–Cu1–N3 96.9(1), N1–Cu1–N5 75.3(1), N3–Cu1–N5 77.0(1), N1–Cu1–O1 162.3(1), N3–Cu1–O1 93.3(1), N1–Cu1–O1\* 92.3(1), N3–Cu1–O1\* 168.5(1); inset: GC-MS trace of organic products with anthracene at  $m/z = 178$ .

## Conclusions

Benzimidazole-based N<sub>3</sub>S ligands support side-on cupric-superoxo complexes as ground state triplets, in contrast with the prevalent view of side-on superoxos as singlets exclusively. The long Cu–O bonds opposite to the strong Cu–N  $\sigma$ -bonds in square pyramidal  $[\text{L}^n\text{Cu}-\eta^2-\text{O}_2]^+$  arise from the small overlap between the Cu  $dx^2-y^2$  and the  $\text{O}_2$   $\pi^*_\sigma$  orbitals, giving rise to the triplet ground states. Despite being strong  $\sigma$ -donors, benzimidazoles give rise to copper complexes that are more electrophilic than their pyridine-based analogues ( $E_{1/2} \sim -170$  mV vs  $\text{Fc}^+/ \text{Fc}$  for  $[\text{L}^n\text{Cu}]^{+/2+}$ ,<sup>7c</sup> compared to  $-470$  mV for pyridine-based N<sub>3</sub>S systems).<sup>6d</sup> This may arise from stabilisation of  $\text{Cu}^+$  complexes by a low-lying LUMO,<sup>7a</sup> setting benzimidazoles apart from related nitrogen donors, and enhancing H-abstraction. The methylthioether in  $[\text{L}^2\text{CuO}_2]^+$  directs H-abstraction from DHA without further oxidation, placing it as a close analogue of the  $\text{Cu}_M$  site of PHM. In this context, the thioethers are weak donors, and may even act as hemilabile ligands. Their role in triplet side-on superoxo complexes in related chemical and biochemical systems awaits further evaluation.

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## Notes and references

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