Published in final edited form as:

Chem Commun (Camb). 2019 June 20; 55(51): 7390–7393. doi:10.1039/c9cc02982f.

Exclusive Imidazole Ligation to $\text{Cu}^{\text{III}}_2\text{O}_2$ and $\text{Cu}^{\text{III}}\text{Cu}^{\text{II}}_2\text{O}_2$ Cores

William Keown^a, Tao A. G. Large^a, Linus Chiang^{a,b}, Erik C. Wasinger^c, T. Daniel P. Stack^a

^aDepartment of Chemistry, Stanford University, Stanford, CA, USA.

^bDepartment of Chemistry, University of the Fraser Valley, Abbotsford, British Columbia, Canada.

^cDepartment of Chemistry and Biochemistry, California State University, Chico, CA, USA.

Abstract

We disclose herein the synthesis and characterization of $\text{L}_2\text{Cu}^{\text{III}}_2\text{O}_2$ and $\text{L}_3\text{Cu}^{\text{III}}\text{Cu}^{\text{II}}_2\text{O}_2$ complexes with nitrogen ligation exclusively from imidazoles for the first time. Their accessibility by direct oxygenation of a L-Cu(I) precursor and the resulting Cu(III) formation inform on the kinetic accessibility and thermodynamic superiority of imidazole in stabilizing Cu(III).

Graphical Abstract

Direct oxygenation of imidazole-ligated Cu(I) generates dinuclear and trinuclear Cu(III) species with exclusive imidazole ligation.

In biological systems, copper is one of the two most used metals for activating dioxygen. The resulting copper-dioxygen ($\text{Cu}_x\text{-O}_2$) assemblies adopt myriad structures with varied nuclearity and degree of O_2 reduction, with the Cu oxidized to the Cu(I) or Cu(II) oxidation states.^{1,2} Despite the diversity of oxidant structures and substrates, these $\text{Cu}_x\text{-O}_2$ active sites retain remarkably similar ligation spheres, with dominant ligation from histidine-derived imidazole groups.^{3,4} As imidazole ligands present a synthetic challenge,^{5–8} synthetic mimics often use Cu(I) complexes with abiological nitrogenous ligation – such as amines,^{9,10} pyridines,^{11,12} pyrazoles,^{13–15} guanidines,^{16,17} and anionic chelates^{18,19} – that frequently oxygenate to Cu(III)-containing species such as dicopper(III) bis- μ -oxide (**O**) or trinuclear bis(μ_3 -oxide)Cu(III)Cu(II)₂ (**T**) species at low temperatures.²⁰ While Cu(III) has been

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here].
See DOI: [10.1039/x0xx00000x](https://doi.org/10.1039/x0xx00000x)

Conflicts of interest

There are no conflicts to declare.

proposed to be operative in biological intermediates,^{21–25} it has yet to be spectroscopically characterized in any system.³ This apparent disconnect between synthetic and biological systems is attributed frequently to the greater basicity of the common synthetic ligands compared to the predominance of imidazole ligation in biology.^{26,27} Recently, we reported that histamine with mixed imidazole and primary amine ligation could stabilize a Cu(III) **O** species at low temperatures,²⁸ and that direct oxygenation of a histamine-Cu(I) complex forms a Cu(III)-containing **T** species directly.²⁹ Whether this reactivity is allowed only by the highly basic amine ligation or whether imidazole alone is capable of stabilizing Cu(III) is unknown, as all literature precedents of direct oxygenation of Cu(I) species with exclusive nitrogen ligation from imidazole yield Cu(II) complexes.

Herein we report the direct and indirect synthesis of an **O_L** species with exclusive imidazole ligation that uses bis(1-*n*-butylimidazole)methane, **L_nBuBIM**, a bidentate, bis-imidazole ligand, to create **O_nBuBIM**. The direct oxygenation of **L_nBuBIM**-Cu(I) forms Cu(III) species **O_nBuBIM** and **T_nBuBIM** at low temperatures. Clean formation of **O_nBuBIM** is also possible through ligand exchange reactions from other preformed **O_L** complexes. Optical monitoring of ligand competition experiments among **O_L** species clearly demonstrates that **L_nBuBIM** is the most donating and thermodynamically stabilizing ligand for Cu(III) investigated to date, despite being less basic than the majority of other **O**-stabilizing ligands.

As most Cu_x-O₂ species formed by oxygenation are strong oxidants with limited lifetimes at 25 °C, synthetic L₂Cu(III)₂O₂ complexes (**O_L**) are assembled generally at low temperatures by direct injection of a L-Cu(I) precursor into an equilibrated O₂ solution.¹⁰ For example, tetramethylpropylenediamine (**L_{TMPD}**) forms **O_{TMPD}** in 90% yield in 1 min at –125 °C from **L_{TMPD}**-Cu(I) and O₂, and near quantitative yields after 5 min. This complex is a convenient synthon for other **O_L** complexes of greater thermodynamic stability by simple ligand exchange; mixed tertiary amine and imidazole ligation can be achieved by addition of 2 equiv of N_α,N_α,N_τ-trimethyl-histamine (**L_{Me3His}**) to **O_{TMPD}**, forming **O_{Me3His}** in high yields by **L_{TMPD}** displacement. As the only difference between these ligands is the substitution of 2 tertiary amines for 2 imidazoles, this ligand exchange evidences thermodynamic stabilization of Cu(III) by *partial* imidazole ligation over peralkylated amine ligation.²⁸

Complete *monodentate* imidazole ligation of an **O_L** species is thermodynamically precluded as addition of 4 equiv. of 1-methylimidazole (**L_{1MeImd}**) to **O_{TMPD}** at –145 °C results in a mixture of the dicopper(II) μ-η²:η²-side-on peroxide, **S_P_{1MeImd}**, species³⁰ and **O_{TMPD}** starting material under all reaction conditions examined (Figure S1). To encourage coordination of only two imidazoles to an **O** species, **L_nBuBIM**, a bidentate, bis-imidazole chelating ligand (Scheme S1/S2) was used in a similar core-capture experiment; 2 equiv of **L_nBuBIM** added to **O_{TMPD}** at –125 °C in 2-methyltetrahydrofuran (2-MeTHF) produces **O_nBuBIM** in *ca.* 5 min (Figures 1 and 2), evidenced by two new intense ligand-to-metal charge transfer (LMCT) transitions at 349 and 251 nm (Figure 2).^{31,32} **O_nBuBIM** is formed in greater than 80% yield established through independent redox titrations with 5,6-isopropylidene ascorbic acid (Figure 2 inset, Figure S7) and ferrocenecarboxylic acid and exhibits a half-life of *ca.* 60 min at –125 °C. Cu K-edge X-ray absorption spectra (XAS)

show a clean pre-edge transition at 8980.7 eV suggestive of Cu(III) (Figure S9).³³ Extended X-ray absorption fine structure (EXAFS) analysis reveals a Cu-Cu distance of 2.78 Å and a Cu-N_{avg.} of 1.94 Å, both distances the shortest known for **O_L** compounds, consistent with sterically undemanding ligation (Table 1, Figure S10). Significantly improved EXAFS fits result from incorporation of Cu-imidazole multiple scattering, supporting direct imidazole ligation to Cu(III) centers. The metrical trends and optical spectra are recapitulated in the DFT optimized structures (Table 1) and their corresponding TD-DFT spectra (Figure S5).^{34,35}

The systematic blue-shifting in optical transitions between the **O_L** species listed in Table 1 is suggestive of stronger donation and bonding from the nitrogenous ligands, the only varying parameter between all the complexes. The accepting orbital of the LMCT is predominantly a Cu-N antibonding orbital. An increase in donation from the nitrogenous ligand increases the energy of this antibonding orbital resulting in a higher energy transition. For example, **O_{Me3His}** (Table 1 entry C: λ_{max} = 380 nm, Cu-N (EXAFS) = 1.97 Å) absorbs at higher energies than **O_{TMPD}** (Table 1 entry A: λ_{max} = 403 nm, Cu-N (EXAFS) = 2.02 Å) as the imidazole bonds closer to the Cu center in comparison to tertiary amines. Similarly, **O_{nBuHis}** (Table 1 entry D: λ_{max} = 363 nm, Cu-N (EXAFS) = 1.96 Å) exhibits blue-shifting and contraction from the propylene diamine (**L_{PD}**) ligated **O** species, **O_{PD}** (Table 1 entry B: λ_{max} = 375 nm, Cu-N (EXAFS) = 2.00 Å), supporting that imidazoles form stronger interactions, presumably through increased σ -donation, than do primary amines to the Cu center.³¹ The optical and structural features of **O_{nBuBIM}** (Table 1 entry E: λ_{max} = 349 nm, Cu-N (EXAFS) = 1.94 Å) are consistent with these findings, as **O_{nBuBIM}** exhibits the most blue-shifted optical transition (Figure S4) and shortest Cu-N bond distances of any **O** species. These observations are further corroborated by DFT and TD-DFT calculations (Figure S5).

The relative thermodynamic stability between imidazole-containing **O** species such as **O_{Me3His}**, **O_{nBuHis}** and **O_{nBuBIM}** is established by ligand competition core capture experiments. Two equiv of **L_{nBuBIM}** sequesters the Cu₂O₂ core from **O_{Me3His}**, with a blue-shift in the optical spectrum (Figure S6), while the reverse ligand exchange reaction between **L_{Me3His}** and **O_{nBuBIM}** is not observed. DFT calculations support these thermodynamic rankings through a computed isodesmic ligand exchange reaction, where **O_{nBuBIM}** is favored over **O_{Me3His}** by *ca.* 8 kcal•mol⁻¹ (Figure 3). Likewise, addition of 2 equiv **L_{nBuHis}** to **O_{nBuBIM}** leads to no significant optical shift, whereas addition of 2 equiv **L_{nBuBIM}** to **O_{nBuHis}** leads to a rapid initial blue-shift of the characteristic LMCT bands, followed by a rapid decay, attributed to concomitant Cu₂O₂ core capture and oxidation of the free primary amine. Overall, this suggests that **O_{nBuBIM}** is more thermodynamically stable than **O_{nBuHis}**, the most stable **O** species previously identified, and further supports the energetic preference of imidazole ligation to Cu(III). Combined with the observation of **O_{nBuBIM}** having the most blue-shifted λ_{max} , these results suggest that exclusive imidazole ligation donates more strongly into the Cu(III) centers than any other combination of neutral, nitrogenous ligation studied and produces the most thermodynamically stable **O_L** species to date.

Direct oxygenation of **L_nBuBIM**-Cu(I) at –125 °C results in a new optical spectrum inconsistent with **O_nBuBIM**, but reminiscent of a L₃Cu(III)Cu(II)₂O₂ trinuclear, **T_L**, cluster with an intense feature at 310 nm and two lesser intensity visible features at 495 and 630 nm (Figure 4).^{11,29,36} The EXAFS data show a characteristically short Cu-Cu_{avg.} distance of 2.66 Å as well as *both* Cu(III) and Cu(II) pre-edges at 8980.4 and 8979.1 eV, respectively, consistent with the compact Cu₃O₂ bis-oxide species, **T_nBuBIM** (Figures 4A, S3, S11, and S12).³⁷ Altering the oxygenation reaction conditions to afford high [O₂]-[Cu(I)] ratios at low overall concentrations, the characteristic 349 nm LMCT of **O_nBuBIM** is observed initially at –145 °C.²⁹ Using its known extinction coefficient from the synthesis by ligand exchange described above, formation by oxygenation is estimated at 15% (Figure S2).

T_nBuBIM forms subsequently over 2 min, resulting in a mixture of two different Cu(III)-containing species formed directly from the oxygenation of a Cu(I)-imidazole precursor (Figure 4B). Taken together, these experiments suggest that exclusive imidazole ligation of Cu(III) is not only thermodynamically favorable, but also kinetically accessible from imidazole-ligated Cu(I) and O₂.^{31,38}

The characterization of **O_nBuBIM** demonstrates that the Cu(III) oxidation state in a Cu_X-O₂ core is viable in an *exclusive* imidazole ligation environment as found in biological systems. What is most surprising is that – despite the greater basicity of synthetic ligand substitutes – the observation of short Cu-N_{imidazole} bond distances, the most blue-shifted λ_{max} for an **O** species to date, and the isodesmic ligand exchange calculations all suggest that, among bidentate ligands, imidazoles are in fact the *most* stabilizing neutral, nitrogenous ligation moiety for these high-valent Cu(III) **O** species. The blue-shift in λ_{max} for **O_nBuBIM** relative to previously reported **O** species is especially noteworthy as the energy ranges for **O** and **SP** LMCT features now overlap such that characterization of Cu(III) vs Cu(II) oxidation states should not be determined by optical transition energies alone. A detailed study of the stereoelectronic compositions of these complexes and how ligation affects their thermodynamic stabilities and optical properties is underway currently.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institutes of Health (GM120187).

Notes and references

1. Mirica LM, Ottenwaelder X and Stack TDP, Chem. Rev., 2004, 104, 1013–1045. [PubMed: 14871148]
2. Elwell CE, Gagnon NL, Neisen BD, Dhar D, Spaeth AD, Yee GM and Tolman WB, Chem. Rev., 2017, 117, 2059–2107. [PubMed: 28103018]
3. Solomon EI, Heppner DE, Johnston EM, Ginsbach JW, Cirera J, Qayyum M, Kieber-Emmons MT, Kjaergaard CH, Hadt RG and Tian L, Chem. Rev., 2014, 114, 3659–3853. [PubMed: 24588098]
4. Holm RH, Kennepohl P and Solomon EI, Chem. Rev., 1996, 96, 2239–2314. [PubMed: 11848828]
5. Himes RA, Park GY, Barry AN, Blackburn NJ and Karlin KD, J. Am. Chem. Soc., 2007, 129, 5352–5353. [PubMed: 17411054]

6. Garcia-Bosch I, Company A, Frisch JR, Torrent-Sucarrat M, Cardellach M, Gamba I, Guell M, Casella L, Que L, Ribas X, Luis JM and Costas M, *Angew. Chem. Int. Ed.*, 2010, 49, 2406–2409.
7. Casella L, Carugo O, Gullotti M, Doldi S and Frassoni M, *Inorg. Chem.*, 1996, 35, 1101–1113. [PubMed: 11666296]
8. Concia AL, Beccia MR, Orio M, Ferre FT, Scarpellini M, Biaso F. d. r., Guigliarelli B, Réglier M and Simaan AJ, *Inorg. Chem.*, 2017, 56, 1023–1026. [PubMed: 28060494]
9. Cole AP, Mahadevan V, Mirica LM, Ottenwaelde X and Stack TDP, *Inorg. Chem.*, 2005, 44, 7345–7364. [PubMed: 16212361]
10. Citek C, Lin B-L, Phelps TE, Wasinger EC and Stack TDP, *J. Am. Chem. Soc.*, 2014, 136, 14405–14408. [PubMed: 25268334]
11. Itoh S, Nagagawa M and Fukuzumi S, *J. Am. Chem. Soc.*, 2001, 123, 4087–4088. [PubMed: 11457163]
12. Jacobson RR, Tyeklár Z, Farooq A, Karlin KD, Liu S and Zubieta J, *J. Am. Chem. Soc.*, 1988, 110, 3690–3692.
13. Jones PL, Jeffery JC, Maher JP, McCleverty JA, Rieger PH and Ward MD, *Inorg. Chem.*, 1997, 36, 3088–3095. [PubMed: 11669961]
14. Wilfer C, Liebhäuser P, Hoffmann A, Erdmann H, Grossmann O, Runtsch L, Paffenholz E, Schepper R, Dick R, Bauer M, Dürr M, Ivanovi -Burmazovi I and Herres-Pawlis S, *Chemistry — A European Journal*, 2015, 21, 17639–17649.
15. Fujisawa K, Ono T, Ishikawa Y, Amir N, Miyashita Y, Okamoto K.-i. and Lehnert N, *Inorg. Chem.*, 2006, 45, 1698–1713. [PubMed: 16471983]
16. Herres-Pawlis S, Flörke U and Henkel G, *Eur. J. Inorg. Chem.*, 2005, 3815–3824.
17. Strassl F, Grimm-Lebsanft B, Rukser D, Biebl F, Biednov M, Brett C, Timmermann R, Metz F, Hoffmann A, Rübhausen M and Herres-Pawlis S, *Eur. J. Inorg. Chem.*, 2017, 2017, 3350–3359.
18. Dhar D, Yee GM, Markle TF, Mayer JM and Tolman WB, *Chem. Sci.*, 2017, 8, 1075–1085. [PubMed: 28572905]
19. Hill LMR, Gherman BF, Aboeella NW, Cramer CJ and Tolman WB, *Dalton Trans.*, 2006, 4944–4953. [PubMed: 17047744]
20. Stack TDP, *Dalton Trans.*, 2003, 10, 1881–1889.
21. Cao L, Caldararu O, Rosenzweig AC and Ryde U, *Angew. Chem. Int. Ed.*, 2018, 57, 162–166.
22. Shiota Y and Yoshizawa K, *Inorg. Chem.*, 2009, 48, 838–845. [PubMed: 19113938]
23. Yoshizawa K, Kihara N, Kamachi T and Shiota Y, *Inorg. Chem.*, 2006, 45, 3034–3041. [PubMed: 16562959]
24. Walton PH and Davies GJ, *Curr. Opin. Chem. Biol.*, 2016, 31, 195–207. [PubMed: 27094791]
25. Keown W, Gary JB and Stack TDP, *J. Biol. Inorg. Chem.*, 2017, 22, 289–305. [PubMed: 27909921]
26. Esguerra KVN and Lumb J-P, *Synthesis*, 2019, 51, 334–358.
27. Sundberg RJ and Martin RB, *Chem. Rev.*, 1974, 74, 471–517.
28. Citek C, Gary JB, Wasinger EC and Stack TDP, *J. Am. Chem. Soc.*, 2015, 137, 6991–6994. [PubMed: 26020834]
29. Gary JB, Citek C, Brown TA, Zare RN, Wasinger EC and Stack TDP, *J. Am. Chem. Soc.*, 2016, 138, 9986–9995. [PubMed: 27467215]
30. Chiang L, Keown W, Citek C, Wasinger EC and Stack TDP, *Angew. Chem. Int. Ed.*, 2016, 55, 10453–10457.
31. Citek C, Herres-Pawlis S and Stack TDP, *Acc. Chem. Res.*, 2015, 48, 2424–2433. [PubMed: 26230113]
32. Henson MJ, Mukherjee P, Root DE, Stack TDP and Solomon EI, *J. Am. Chem. Soc.*, 1999, 121, 10332–10345.
33. DuBois JL, Mukherjee P, Stack TDP, Hedman B, Solomon EI and Hodgson KO, *J. Am. Chem. Soc.*, 2000, 122, 5775–5787.
34. Goswami VE, Walli A, Forster M, Dechert S, Demeshko S, Holthausen MC and Meyer F, *Chem. Sci.*, 2017, 8, 3031–3037. [PubMed: 28451371]

35. All attempts to stabilize OnBuBIM with a monodeprotonated, anionic form of LnBuBIM (i.e. deprotonation of OnBuBIM with exogenous base or ligand exchange with deprotonated LnBuBIM result in decomposition of the O species. Addition of acids or H-atom donors to O_nBuBIM in attempts to protonate the potentially deprotonated ligand did not return isolated ligand. See reference 34._nBuBIM
36. Cole AP, Root DE, Mukherjee P, Solomon EI and Stack TDP, Science, 1996, 273, 1848–1850. [PubMed: 8791587]
37. Decamethyl ferrocene titrations suggest ca. 80% formation (Figure S8) with the assumption of trinuclear as a one-electron oxidant.
38. Chen P and Solomon EI, J. Am. Chem. Soc., 2004, 126, 4991–5000. [PubMed: 15080705]

Figure 1.

Templated core capture synthetic methodology to generate O_{nBuBIM} .

Figure 2.

UV-Vis absorption spectra of O_{nBuBIM} ($\lambda_{\text{max}} = 349, 251 \text{ nm}$, red trace) generated from O_{TMPD} (black trace) at -125°C . $[\text{Cu}] = 0.9 \text{ mM}$, 0.1 cm path, 2-MeTHF. Inset: titration of the 349 nm feature of O_{nBuBIM} by ascorbic acid.

Figure 3.

DFT calculated isodesmic ligand exchange reactions. Optimized at the CAM-B3LYP/6-31g*/SMD(THF) level with def2tzvp and DKH2 relativistic corrections for single point energy calculations. Red X over the reverse reaction indicates that reversibility was not observed experimentally even in presence of excess ligand.

Figure 4.

A) Oxygenation of $L_{nBuBIM}-Cu(I)$ ($[Cu] = 0.9\text{ mM}$, 0.1 cm , 2-MeTHF, $-125\text{ }^{\circ}C$). Inset: Titration of the 310 nm feature of T_{nBuBIM} by incremental addition of cobaltocene (Figure S8). B) Oxygenation of $L_{nBuBIM}-Cu(I)$ ($[Cu] = 0.1\text{ mM}$, 1 cm , 4:1 2-MeTHF:T THF, $-145\text{ }^{\circ}C$). Beginning O_{nBuBIM} formation is shown in red with subsequent T_{nBuBIM} formation in grey/black.

Table 1.Physical Properties of Relevant O_L Complexes.

Entry	Compound ^[a]	UV-Vis: λ_{max} , nm; (ϵ , mM ⁻¹ cm ⁻¹) ^{a,b,c,d}	Metrical parameters: EXAFS, Å ^[d] ; (DFT, Å ^[e])		
			Cu-Cu	Cu-O	Cu-N
A	O _{TPD} ^[b]	403 (29.4), 302 (18.7)	2.85 (2.77)	1.84 (1.77)	2.02 (1.97)
B	O _{TPD} ^[b]	375 (22.6), 278 (21.0)	2.77 (2.66)	1.86 (1.76)	2.00 (1.91)
C	O _{Me₃His} ^[c]	380 (30.2), 280 (24.5)	2.80 (2.72)	1.82 (1.77)	1.97 (1.95, 1.89)
D	O _{nBuHis} ^[c]	363 (27.8), 262 (34.2)	2.78 (2.69)	1.82 (1.77)	1.96 (1.91, 1.88)
E	O _{nBuBIM}	349 (24.1), 251 (35.1)	2.78 (2.69)	1.84 (1.76)	1.94 (1.89)

^[a] SbF₆⁻, 2-MeTHF, -125 °C, yield corrected extinction coefficients.^[b] See reference 10 for further characterization.^[c] See reference 28 for further characterization.^[d] Resolution $\approx \pm 0.01$ Å.^[e] Optimized at the CAM-B3LYP/6-31g^{*}/SMD(THF) level. Def2TZVP basis sets recapitulate the same trend.