JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b10833 • Publication Date (Web): 06 Dec 2017

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Thermodynamics of a μ-oxo Dicopper(II) Complex for Hydrogen Atom Abstraction

Ghazanfar Ali, Peter E. VanNatta, David A. Ramirez, Kenneth M. Light, Matthew T. Kieber-Emmons*

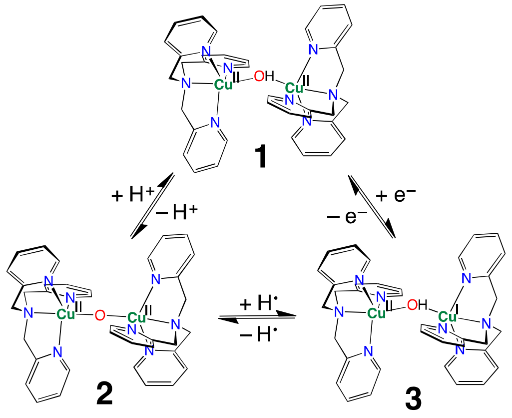
Department of Chemistry, University of Utah, Salt Lake City, UT 84112-0850

Supporting Information Placeholder

ABSTRACT: The mono-μ-hydroxo complex $\{[Cu(tmpa)]_2\text{-}(\mu\text{-}OH)\}^{3+}$ (**1**) can undergo reversible deprotonation at –30°C to yield $\{[Cu(tmpa)]_2\text{-}(\mu\text{-}O)\}^{2+}$ (**2**). This species is basic with a pKa of 24.3. **2** is competent for concerted proton-electron transfer from TEMPOH, but is an intrinsically poor hydrogen atom abstractor (BDFE(OH) of 77.2 kcal/mol) based on kinetic and thermodynamic analyses. Nonetheless, DFT calculations experimentally calibrated against **2** reveal that $[Cu_2O]^{2+}$ is likely thermodynamically viable in copper-dependent methane monoxygenase enzymes.

A major contemporary challenge is the selective catalytic conversion of fossil feedstocks. Methane, the principle component of natural gas, poses a particular challenge because of its strong C-H bonds and tendency to be over oxidized to carbon dioxide. Advances in extraction from underground sources has dramatically increased access to methane, and thus efficient conversion of methane into easily transportable products, such as methanol, is a significant need. Methanotrophic organisms are well known to consume methane through the action of methane monoxygenase enzymes that catalyze the direct oxidation of methane to methanol;[1] however, the nature of the active site in copper-dependent methane monoxygenase (pMMO) has eluded unambiguous assignment.[2] Mechanistic insight for pMMO has come from computational[3,4] and model studies, of which copper exchanged zeolites have been highly instructive due to good selectivity for oxidation of methane to methanol and ability to function under catalytic conditions.[5] Under stoichiometric conditions, $[Cu_2O]^{2+}$ species[6] and $[Cu_3O_2]^{2+}$ species[7] have been implicated as the active oxidants, which parallels proposals in copper dependent MMOs.[8] The dicopper(II) μ-oxo ($[Cu_2O]^{2+}$) species has been of particular recent interest (Figure 1);[9,10] however, no experimental thermodynamic information has been available to validate the feasibility for initial hydrogen atom abstraction from strong C-H bonds. Since this putative intermediate has not been trapped in pMMO, model studies are required to evaluate factors that would enable the initial hydrogen atom abstraction. Herein we report $\{[Cu(tmpa)]_2\text{-}(\mu\text{-}OH)\}^{3+}$ (**1,** tmpa = tris(2-pyridylmethyl)amine), which could be reversibly deprotonated to generate a $[Cu_2O]^{2+}$ core which is functional for H-atom abstraction from exogenous substrates (Scheme 1). This finding enables the thermodynamic and kinetic evaluation of the feasibility of a $[Cu_2O]^{2+}$ core as the functional oxidant in pMMO.

Scheme 1. Interconversion of dicopper-O(H) complexes reported herein.



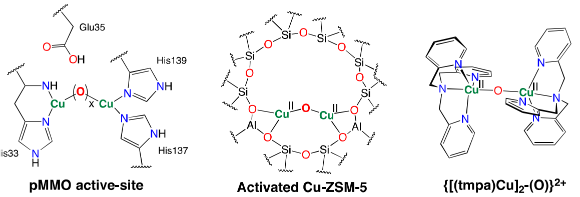


Figure 1. Comparison of the active-site architecture in pMMO with the defined $[Cu_2O]^{2+}$ cores in Cu-ZSM-5 and in the present study.

Complex **1** was prepared as the OTf^- salt (OTf = trifluoromethansulfonate) by addition of $CuOTf_2$ to tmpa in methanol under nitrogen, followed by addition of excess H_2O and NEt_3 to generate a blue product (62% yield, see Supporting Information for details). Crystals suitable for X-ray diffraction analysis were generated by vapor diffusion of diethyl ether into the methanol solution that yielded the dicopper(II) mono-μ-OH complex **1** (Figure 2). Assignment of the bridge as an OH group was based on the overall charge of the cation which was +3 and on the Cu-O(H) bond lengths of 1.918(2) Å and 1.915(3) Å, consistent with those of mono-μ-OH complexes which range from 1.87 Å to 1.93 Å (Table S2). The coordination environment about the copper is trigonal bipyramidal with the tmpa amine apical, the pyridine arms in the equatorial positions with an average Cu-N(py) distance of 2.084 Å, and the OH^- occupying the basal axial position. The Cu-O(H)-Cu core is bent, with the Cu-O(H)-Cu angle at 144.50(14)°.

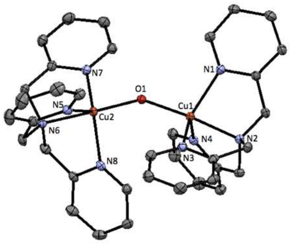


Figure 2. ORTEP of the trication of **1** from X-ray crystallographic data at 35% ellipsoid probability.

Further evidence for assignment of **1** as a mono-μ-OH comes from FTIR where a ν(O-H) peak was observed at 3450 cm^{-1} that downshifts to 2560 cm^{-1} in the OD isotopologue, consistent with that expected (2510 cm^{-1}) from reduced mass calculations on an isolated harmonic oscillator. Complex **1** is EPR silent, yet displays a paramagnetic ^{1}H-NMR spectrum (Figure S8), which indicates an integer spin electronic structure derived from two magnetically coupled d^9 Cu(II) ions, and thus a dinuclear geometric structure in solution. Variable temperature ^{1}H-NMR (Figure S4) revealed anti-Curie magnetic behavior resultant from an antiferromagnetically coupled ground state with a low-lying ferromagnetically coupled excited state. This behavior was modeled using the effective spin Hamiltonian $H = -2JS_1 \cdot S_2$ to yield a magnetic coupling parameter $-2J = -223\ cm^{-1}$ in agreement with that expected from the 144° Cu-O-Cu angle (Figure S3). The electronic absorption spectrum of complex **1** in acetonitrile (MeCN, Figure 4) displays features at 290 nm (2750 $M^{-1}cm^{-1}$), and 350 nm (5460 $M^{-1}cm^{-1}$) that are assigned as OH→Cu(II) ligand-to-metal charge transfer transitions and 822 nm (320 $M^{-1}cm^{-1}$) Cu(II) d→d transitions respectively on the basis of energy and intensity.

The reduction of complex **1** was studied by cyclic voltammetry (CV). Complex **1** was prepared at 0.52 mM in MeCN with 0.1 M $TBAPF_6$ (tetrabutylammonium hexafluorophosphate) as supporting electrolyte. At –30°C, a reversible 1 e^- wave was observed at –0.48 V vs Fc/Fc^+ (Figure 3) and a second, irreversible wave was observed at –0.70 V vs Fc/Fc^+ (Figure S6). These waves are assigned as the $Cu_2^{II,II/II,I}$ couple and tentatively the $Cu_2^{II,I/I,I}$ couple respectively based on comparison to $[Cu_2(BPMAN)(\mu\text{-}OH)](OTf)_3$ (BPMAN = 2,7-[bis(2-pyridylmethyl)aminomethyl]-1,8-naphthyridine), where an irreversible anodic half wave was observed at –0.44 V vs Fc/Fc^+ and an irreversible cathodic half wave was observed at –0.78 V vs Fc/Fc^+.[11]

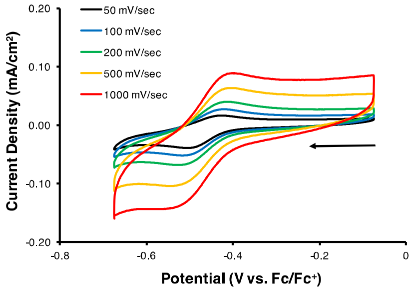


Figure 3. Cyclic voltammograms of **1** in MeCN at –30°C with scan direction denoted by the arrow.

Deprotonation of complex **1** yielded a new, thermally sensitive species **2**. Specifically, addition of one equivalent of triisobutyl-substituted Verkade's superbase (2,8,9-Triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane) to **1** in MeCN at –30°C (Figure S9) results in appearance of a new optical feature at 290 nm (2750 $M^{-1}cm^{-1}$). This reaction was reversible; addition of [LutH](OTf) (LutH = 2,6-dimethylpyridin-1-ium) resulted in reappearance of the optical bands associated with **1**. **(**Figure S9**)**. **2** displays a diamagnetic ^{1}H-NMR spectrum (Figure S8) and is EPR silent, which together suggest an integer spin electronic structure and thus a dinuclear geometric structure. These data suggest formulation of **2** as the dicopper(II)-μ-O adduct $\{[Cu(tmpa)]_2\text{-}(\mu\text{-}O)\}^{2+}$.[12]

Since the $[Cu_2O]^{2+}$ core of **2** has been implicated as analogous to the active oxidant in pMMO, we sought experimental insight into the thermodynamics for hydrogen atom abstraction by **2**. Thus, we measured the pKa of **1** at –30°C in MeCN. Titration of **1** with triisobutyl-substituted Verkade's superbase (pKa = 33.53) resulted in stoichiometric conversion of **1** into **2**, indicating a weaker base would be required to access an equilibrium condition

(Figure S9). No reaction was observed with NEt_3 ($pKa = 18.46$), but sigmoidal shaped conversion of **1** to **2** was observed for titration of **1** with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, $pKa = 24.33$, Figure 4). This equilibrium behavior was modeled to yield a room temperature corrected pK_a of 24.3 ± 1.9 for complex **1**. This is much more basic than a recently reported dicopper(II)-μ-O adduct in which the pKa was determined to be between 4.5 and 14,[13] but is similar to a dicopper(II)-superoxo adduct, which displayed a pKa of 22.2,[14] and suggests an electron rich oxo moiety.

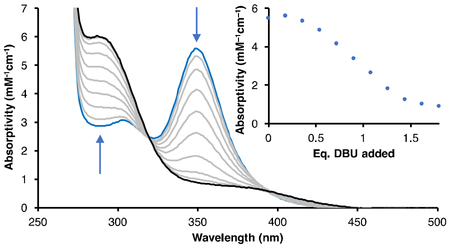


Figure 4. Titration of **1** (—) with DBU at –30°C in MeCN resulting in formation of **2** (—); Inset: titration monitored at 350 nm.

Using the thermodynamic parameters $E^{1/2}$ (–0.48 V vs Fc/Fc^+) and pKa (24.3) determined above, a thermodynamic cycle was constructed (Figure 5) that allows determination of the BDFE of the O–H bond of **3**. This value is derived according to the equation:

$$\mathrm{BDFE(OH)} = 1.37\mathrm{pK_a} + 23.06\mathrm{E}^0 + C_G$$

where C_G represents the $H^+/H^\bullet$ reduction potential in MeCN (54.9 kcal/mol).[15] $E^{1/2}$ as an approximation of E^0 yields a BDFE(OH) of 77.2 ± 2.3 kcal mol^{-1}. Density functional theory calculations were performed to benchmark this value. Specifically, an isodesmic H-atom abstraction from 2,4,6-(tri-tert-butyl)phenol was calculated. This phenol has a known –OH BDFE (80.3 kcal mol^{-1}), which yields a calculated BDFE(OH) in **3** of 81.6 kcal mol^{-1}, in reasonable agreement with the experimentally determined value. This value is substantially lower than that in Cu-ZSM-5 where the analogous BDFE is predicted on the basis of DFT to be 90 kcal mol^{-1}.[6]

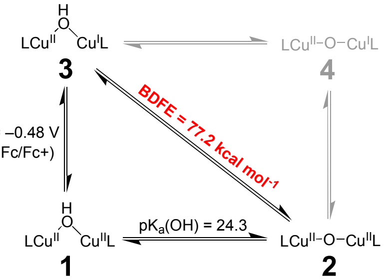


Figure 5. Thermodynamic cycle which relates the oxidation of complex **1** to the pKa of complex **1** to yield the BDFE(OH) of complex **3**. The hypothetical species **4** is illustrated in gray.

Despite the weaker BDFE of **2** compared to Cu-ZSM-5, we were encouraged because **2** decomposes slowly to unidentified products at –30°C in MeCN with a $t_{1/2}$ of ~3.5 hrs. We tested the reactivity of **2** towards weak C-H bonds at –30°C, and found **2** reacted very slowly with 1,4-cyclohexadiene (BDFE 72.9 kcal mol^{-1}) to generate benzene (75% yield by NMR). Nonetheless, **2** was moderately reactive towards the O-H bond of TEMPOH to generate $TEMPO^\bullet$ in quantitative yield by EPR spin quantitation (Figure S16). Kinetic analysis of the reaction of **2** generated in situ with 2 eq DBU and TEMPOH in MeCN (Figure 6)[16] yielded an $\Delta H^\ddagger$ of 5.3 ± 2.8 kcal mol^{-1} and a $\Delta S^\ddagger$ of -44 ± 11 cal mol^{-1} which translates to a $\Delta G^\ddagger$ (298 K) of 18 ± 2.8 kcal mol^{-1}. While these kinetics are complicated by subsequent side-reactions (see Supplementary Information for details), we verified that these kinetic parameters are probing the H-atom abstraction by reaction with TEMPOD, which yielded a small, primary kinetic isotope effect (KIE = k_H/k_D) of 1.6 ± 0.3. The barrier and KIE of this reaction reflect a concerted hydrogen atom transfer (HAT) process rather than an initial proton or electron transfer, which are disfavored due to the pKa and E^0 of TEMPOH. A concerted HAT would require formation of an encounter complex, which the large entropy of activation and small enthalpy of activation supports. The small KIE further supports this notion, indicating a transition state late with respect to H-atom transfer. Thus, the rationale for the lack of reactivity towards weak C-H bonds is the higher steric demands of the C-H substrates. To corroborate the role of sterics, DFT calculations were performed on **2**. DFT predicts an antiferromagnetically coupled and linear $[Cu_2O]^{2+}$ core to be the lowest energy structure after spin purification of the broken-symmetry singlet (Figure S20). Evaluation of the space-filling model of **2** suggests that the pseudo-C_{3v} symmetric copper coordination environment with interdigitated ligand arms precludes access to the $[Cu_2O]^{2+}$ core (Figure S18).

The weak BDFE of **3** suggests that even in absence of sterics, the $[Cu_2O]^{2+}$ core of **2** is not intrinsically very reactive; for example, the minimum barrier for reaction of **2** with methane (BDFE(CH) 105 kcal mol^{-1}) would be ~28 kcal mol^{-1}. This is in contrast to the reactivity of the $[Cu_2O]^{2+}$ core demonstrated by Cu-ZSM-5, albeit with its abiological ligand set, and thus we questioned whether this type of core could function in the biological context of pMMO. To address this question, we applied our calibrated DFT methodology to the BDFE(OH) of an active site model of pMMO (Figure S19). In pMMO, the Cu-Cu distances are relatively short (2.58 – 2.71 Å, Table S4) compared to binuclear Type 3 Cu proteins in the deoxy state (2.2 – 4.5 Å),[17] which implies the protein constrains the Cu-Cu distance. In our computational model containing the $[Cu_2O]^{2+}$ core, the constraints lead to a Cu-Cu distance of 3.475 Å, comparable to previous oxo-pMMO models (Table S5), which further leads to a bent Cu(II)-O-Cu(II) core (165.1°). In pMMO, this core is much more accessible than in **2** due to the bidentate coordination environment about each copper. Using our calibrated DFT methodology and benchmarked by **3**, we computed an isodesmic reaction with 2,4,6-(tri-tert-butyl)phenol on the pMMO model. On the singlet surface, the BDFE(OH) of the pMMO model is predicted to be 89.9 kcal mol^{-1} (Figure S21). While our methodology slightly overestimates this value compared to experiment, it nonetheless indicates that a putative $[Cu_2O]^{2+}$ core is likely strong enough to abstract an H-atom from methane in pMMO. An unresolved question is what specific geometric and electronic structure factors would lead to the enhanced HAT thermodynamics of a $[Cu_2O]^{2+}$ core in pMMO? Towards that end, the Cu-O-Cu bend plays a minor role (~2 kcal/mol) based on DFT of **2** (Figure S21 & S22).[18] Other factors will likely include a combination of charge and nature of the donors, coordination number, and geometry, all of which are yet to be explored.

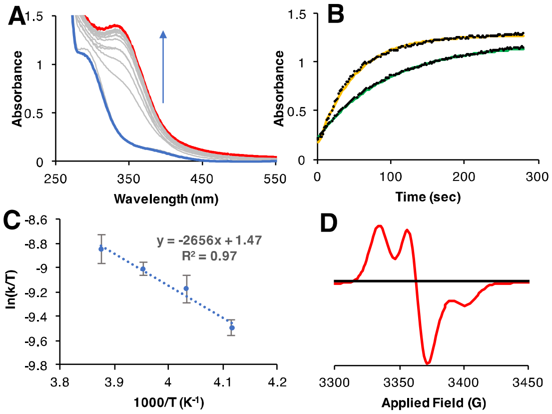


Figure 6. **A:** Reaction of 10 eq TEMPOH with **2** (—) prepared in situ by addition of 2 eq DBU to **1** in MeCN at –30°C, time between lines is 10 sec; **B:** change in A_{350} vs time for reaction of **2** with TEMPOH (—) and TEMPOD (—); **C:** Eyring analysis of reaction with TEMPOH; **D:** EPR before (—) and after (—) reaction of **2** with TEMPOH.

In summary, we have synthesized a dicopper(II)-µ-OH adduct that enabled for the first time the determination of hydrogen atom abstraction thermodynamics of a $[Cu_2O]^{2+}$ species. While it has been generally held that these species would be intrinsically reactive,[8] the oxo group is highly basic and thus bears considerable electron density, which leads to weak HAT ability. Thus, the pMMO active site must generate a less electron rich $[Cu_2O]^{2+}$ moiety to drive HAT from the strong C-H bonds of methane. Ongoing studies are aimed to elucidate factors that enable this process.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge via the internet at http://pubs.acs.org.

Crystallographic data (cif).

Detailed materials and methods, crystallographic information, determination of the pKa of 1, and computational methods. (pdf).

AUTHOR INFORMATION

Corresponding Author

matthew.kieber-emmons@utah.edu

ORCID

Matthew T. Kieber-Emmons: 0000-0002-6357-5579

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENTS

The authors acknowledge Nathan Buehler for the synthesis and crystallization of **1**, Asmita Shrestha for early observations on the deprotonation of **1,** and Arif Atta for solving the structure of **1**. Computer time was provided by the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation grant number ACI-1053575 (TG-CHE130047), and the Center for High Performance Computing at the University of Utah.

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