Computational strategies to probe CH activation in dioxo-dicopper complexes†

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We employ density functional theory and energy decomposition analysis to probe the mechanism of CH activation in dioxo-dicopper complexes. The electrophillicity of monodentate N-donor ligands coordinated to Cu is systematically varied to examine the response of barriers to the two proposed pathways – one-step oxo-insertion and two-step radical recombination. Electron-withdrawing ligand stabilize the oxo-insertion transition state via charge transfer interactions, and therefore lead to lower barriers. On the other hand, barriers to the CH activation step in the radical recombination mechanism exhibit almost no dependence on N-donor electrophilicity. Based on the similarities between calculated and experimental Hammett relationships, the oxo-insertion pathway appears to be the preferred mechanism of CH activation in dioxo-dicopper catalysts.

1 Introduction

The dioxo-dicopper ([Cu₂O₂]²⁺) catalytic center is of significant scientific interest since it constitutes the active center of several enzymes¹ and their synthetic mimics²–⁵ which can selectively oxidize CH bonds. It is believed to constitute the active center of the selective methane hydroxylation enzyme, particulate methane monooxygenase (pMMO), although the characterization of the active site is a long-standing challenge.⁶–⁹ and heterogeneous catalysts such as Cu-containing zeolites.¹⁰,¹¹ The [Cu₂O₂]²⁺ core also serves as a test bed for multireference quantum chemical methods since its common isomeric form (µ – η² : η² peroxo, or P) is an open-shell system, which cannot be accurately represented using single-reference methods such as density functional theory (DFT).¹²–¹⁵

In spite of several experimental and computational studies of [Cu₂O₂]²⁺-containing enzymes and synthetic complexes, there is little consensus regarding the mechanism of CH activation. Broadly, one of two pathways is proposed based on mechanistic similarities observed with electrophilic aromatic substitution.¹⁶ – (a) one-step oxo-insertion involving simultaneous C–H and Cu–O bond-breaking and C–O and O–H bond making,¹⁷–²² and (b) two-step radical recombination in which the first step corresponds to C–H breaking to form a methyl radical that rebinds and extracts OH in the second step.²³–²⁷ The reader is directed to a recent study by Da Silva et al.²⁶ for an extensive overview of mechanistic efforts, particularly towards understanding CH activation with model pMMO complexes. Based on a comparison of singlet and triplet pathways for the radical mechanism, computational studies propose the possibility of spin-crossover to²⁸ the potential energy surface offering a lower barrier.²⁵,²⁶ The possibility of spin-crossover, coupled with limited DFT accuracies – for describing spin-state energetics in transition metal complexes,²⁹,³⁰ multireference characteristics, and relativistic effects¹⁵ – makes it difficult to analyze and interpret mechanisms based purely on DFT energies.

We propose an additional step to the calculation of singlet and triplet pathways for oxo-insertion and radical recombination. This work is inspired by experimental studies with synthetic dicopper complexes, which analyze kinetics response to systematic modifications in the substrate. Mahapatra et al.¹⁶ demonstrate that the barrier to intramolecular benzyl activation is lowered upon substituting more electron-donating ligands at the para position of benzyl. They conclude, based on the slope of the resulting Hammett plots, that CH activation is a type of electrophilic aromatic substitution that proceeds either via radical rebound or oxo-insertion pathways. Stack and co-workers³¹,³² also show, with both ethylenediamine and imidazole-based dicopper catalysts, that the substitution of substrate phenolates with electron-donating ligands enhances reaction rates.

However, the range of observed experimental barriers obtained upon varying ligand nucleofility in these studies is very narrow (< 10 kJ/mol). In general, density functional approximations cannot meaningfully resolve energy differences in such a narrow range. Although Cramer and Pak use hybrid quantum mechanics/molecular mechanics (QM/MM) calculations to demonstrate the possibility of a radical-based pathway by varying ligands attached to the substrate, the range of barriers they calculate is also narrow (7 kJ/mol).²⁷ We propose an alternative strategy that instead probes barrier response to ligand substitutions in the catalyst. Since electron-donating groups in the substrate lower barriers, the governing hypothesis is that a similar but stronger response can be achieved by enhancing the electron-withdrawing character of all N-donors in the catalyst. The response of the two proposed pathways to variations in the catalyst are quantitatively compared with experimental Hammett plots¹⁶,³¹–³⁴ in order to

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facilitate the interpretation of the true mechanism of CH activation.

Using CH₄ and [Cu₂(NH₃)₄O₂]²⁺ as the model substrate and catalyst, respectively, the singlet and triplet oxo-insertion and radical-based pathways for transformation to CH₃OH are calculated using DFT. With these geometries as templates, dioxodicopper catalysts containing amine and imidazole-based N-donors of varying electrophilicity are constructed. The response of singlet CH activation barriers for both pathways are contrasted. Since partial charge separation occurs in the o xo-insertion transition states, appreciable barrier lowering is observed with strong electron-withdrawing ligands. Energy decomposition analysis (EDA) shows that barrier-lowering is dominated by stabilizing charge transfer interactions between the substrate and catalyst. On the other hand, radical barriers are invariant to changes in N-donor electrophilicity. A comparison of Hammett plots with experimental dicopper kinetics strongly supports the one-step oxo-insertion mechanism as the preferred pathway for CH activation. Going forward, this study can also be combined with complementary dicopper-catalyzed oxidation experiments wherein the mechanism is determined through the presence or absence of rate sensitivity to N-donor electrophilicity.

2 Methods

2.1 Model Systems and Mechanisms

All calculations are carried out using the commercial ab initio quantum chemistry code, Q-Chem 5.1. [Cu₂(NH₃)₄O₂]²⁺ is chosen as the model complex and CH₄ as the model substrate to calculate CH activation pathways in the gas phase. While the dioxodicopper center, [Cu₂O₂]²⁺, can be coordinated in multiple ways, experimentally synthesized complexes typically exhibit two isomeric forms – the μ−η¹:η² peroxo (P), and the bis(μ-oxo) (O) configurations. The relative prevalence of either isomer and equilibrium between the two isomers are determined not only by the ligand field but also experimental conditions such as solvent and choice of counterions. In this study, both O and P isomers are constructed in the singlet (S) and triplet (T) spin states.

The question of choosing an appropriate level of theory for this system is not a trivial one. The [Cu₂O₂]²⁺ core with a peroxo linkage (P isomer), owing to the partially occupied d⁹ state of each Cu, is a quintessential multireference system for testing various single- and multireference quantum chemical approaches. Using various single-reference (including DFT) and multireference methods, Gagliardi and coworkers show that the difference between calculated O-P isomerization energies for [Cu₂(NH₃)₄O₂]²⁺ spans a very wide range (>150 kJ/mol). A more recent study by Liakos and Neese demonstrates, using the [Cu₂(en)₂O₂]²⁺ complex, that solvent and relativistic contributions are more important than correlation effects.

We choose the ωB97X-D functional, since hybrid functionals typically provide a reasonable description of transition states and activation barriers. We also choose a small basis set – the double-ζ 6-31G* basis set – motivated by the need to rapidly screen several catalysts to determine barrier responses. Since the choice of functional and basis set raises the question of accuracy of O-P isomerization energies, we attempt to benchmark our calculations with [Cu₂(NH₃)₂O₂]²⁺ and [Cu₂(en)₂O₂]²⁺ (ESI). As described earlier, there is little consensus between various wavefunction methods for [Cu₂(NH₃)₄O₂]²⁺ isomerization energies that precludes reliable benchmarking. However, the ωB97X-D/6-31G* O-P isomerization energy for the analogous complex with bidentate ligands, [Cu₂(en)₂O₂]²⁺, is only 13 kJ/mol lower than the LPNO-CCSD reference. Moreover, interconversion from P to O is an essential step for CH activation, as described in Section 3. This means that, without loss of generality, the O isomer can be used as the reference catalyst configuration for all mechanistic studies. The initial state (or reactant) energies for pathways beginning with the P isomer can then be incorporated as on-top corrections calculated using highly accurate multireference methods. A preliminary analysis of solvation effects is also carried out for the [Cu₂(NH₃)₄O₂]²⁺ complex (ESI). The calculated bond distances at the active site, shown in Table 1, are in good agreement with prior computational studies of similar systems and varying levels of theory.

Wavefunction stability analysis is carried out to verify whether electronic structure calculations converge to stable minima with respect to spin orbital perturbations. Spin-pure energies are calculated from broken-symmetry (BS) solutions using the spin-correction scheme proposed by Yamaguchi et al.. For the bare catalyst, the electronic structure of the closed-shell O isomer is stable while spin correction is necessary to describe the P isomer. Spin-corrections are also necessary for most singlet transition states (TSs) and some triplet TSs, which exhibit contamination from higher spin states.

TS geometries for the single-step o xo-insertion and the two-step radical recombination pathways are calculated using a combination of the double-ended freezing string method and Hessian-free optimization. All TSs are verified using vibrational analysis and all potential energies reported in this study are zero-point corrected. In addition to vibrational analysis, intrinsic reaction coordinate (IRC) calculations are carried out to verify whether perturbation of the TS along the reaction coordinate leads to the correct reactant and product (or intermediate) geometries.

2.2 Ligand Effects

With the goal of probing (singlet) barrier response to ligand electrophilicity, a suite of model O catalysts are created by successively substituting monodentate NH₃ with two classes of ligands as shown in Table 2:

1. Amine-based N-donors (NH₂X₃am): X₃am = OCH₃, CH₃, H (parent system), CF₃, and NO₂, in increasing order of X₃am Hammett parameter calculated for para-substituted benzoic acids.
2. Imidazole-based N-donors (C₆H₁₃N₃X₃am): X₃am = OCH₃, CH₃, H, CF₃, and NO₂, where X₃am is substituted at the C atom between the two N atoms.

These systems are chosen largely because stable O isomers with substituted amines and imidazoles are reported in experimental
Table 1 [Cu_2(NH_3)_4O_2]^{2+} singlet (S) and triplet (T) model complexes corresponding to \( \mu - \eta^2 : \eta^2 \) peroxo (P) and the bis(\( \mu \)-oxo) (O) configurations of the [Cu_2O_2]^{2+} core, along with relevant bond distances and (average) angles, calculated in the gas phase using \( \omega \)B97X-D/6-311G* level of theory. (Cu: ochre, O: red, N: blue, H: white, C: cyan)

<table>
<thead>
<tr>
<th>Isomer/Spin</th>
<th>Geometry</th>
<th>Bond length (Å)</th>
<th>Bond angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cu-Cu Cu-O Cu-N O-O N-Cu-N</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>S</td>
<td>3.445 1.867 1.970 1.437 108.8</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td></td>
<td>3.290 1.915 1.982 1.467 104.7</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>S</td>
<td>2.698 1.756 1.939 2.249 98.1</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td></td>
<td>2.790 1.810 1.965 2.307 100.6</td>
<td></td>
</tr>
</tbody>
</table>

literature. Imidazole-coordinated copper moieties are also frequently found in enzymes.

For each complex, the geometry and connectivity of the core (Cu, O, N) are fixed at the values determined for the parent [Cu_2(NH_3)_4O_2]^{2+} system. The substrate positions are also fixed in TS calculations. TSs and ISs are then determined using geometry optimization and verified with vibrational analysis calculations. This strategy dramatically reduces computational effort by eliminating the need for repeated TS searches. It also allows us to examine purely electronic interactions by minimizing geometric or strain energy differences across systems.

Only one H atom is substituted per NH_3 group rather than all three in the amine N-donor systems in order to minimize steric effects and ligand-ligand orbital interactions. It becomes challenging to isolate and examine barrier responses purely to changes in ligand electrophilicity in the presence of orbital overlap between adjacent ligands. For this reason, N-donors such as CN-substituted amines and imidazoles are not included in this study.

2.3 Energy Decomposition Analysis

While DFT calculations determine the electronic structure and energy of the substrate-catalyst system as a whole, a physically meaningful description of the interacting system emerges when the electronic energy is broken down into its constituent interactions. Energy decomposition analysis (EDA) is an elegant technique that determines intermolecular interactions between two or more fragments by decomposing binding energy into components such as charge transfer, electrostatics, dispersion, polarization, and Pauli repulsion. We utilize the second-generation absolutely-localized molecular orbital (ALMO) flavor of EDA, in which the interaction energy (\( E_{\text{INT}} \)) is given by

\[
E_{\text{INT}} = E_{\text{PRP}} + E_{\text{FRZ}} + E_{\text{POL}} + E_{\text{CT}}
\]  

(1)

\( E_{\text{PRP}} \) is the energy required to prepare the fragments. Since it contributes to less than 1 kJ/mol for any system, \( E_{\text{PRP}} \) is neglected in the ensuing analysis. Frozen interactions (\( E_{\text{FRZ}} \)), or the energy difference between unrelaxed wavefunctions in the interacting fragments and isolated fragments, is further decomposed into permanent electrostatics or Coulombic interactions (\( E_{\text{ELEC}} \)), Pauli repulsion (\( E_{\text{PAULI}} \)) caused by reduction in volume occupied by electrons upon bringing fragments close together, and dispersion (\( E_{\text{DISP}} \)) energies. Polarization corresponds to the energy lowering caused by relaxing the frozen orbitals of each fragment (\( E_{\text{POL}} \)) in the presence of the other, and the charge transfer term (\( E_{\text{CT}} \)) is obtained from further interfragment relaxation of the orbitals.

EDA is carried out by partitioning the catalyst-substrate system into the dicopper complex and methane fragments. For both the singlet oxo-insertion and radical formation steps, the differences in EDA components between the transition states (TS_{oxo} for oxo-insertion and TS_{1} for first step of radical recombination) and initial state (IS) are calculated. All EDA calculations include corrections for basis set superposition error. The impact of varying N-donor electrophilicity on the electronic structure of the dicopper core and activation barriers are subsequently examined.

2.4 Hammett Relationships

The construction of Hammett plots that relate substituent philicity to observed reaction rates is a widely accepted method to exper-
to contrast barrier trends with experimental studies. Moreover, a Hammett analysis provides us with the most direct means of rationalizing energy differences: 

$$
\rho = \frac{\Delta E_{is} - \Delta E_{ts}}{2.303 R T} \quad \text{(2)}
$$

where $i = \text{TS}_\text{oxo}$ or $\text{TS}_1$, and $T = 193 K$ for amines and $T = 148 K$ for imidazoles. Hammett parameters are plotted along the x-axis. While $\sigma^+_p$ is used in both experimental studies since it is more accurate for a phenolate substrate than $\sigma_p$, the appropriate parameter type ($\sigma_m$, $\sigma_p$, or $\sigma^+_p$) for catalyst substitutions is not known. Therefore, all three sets of parameters are employed to plot Hammett relationships for comparison with experiment and mechanistic interpretation.

### 3 CH Activation

Calculated TSs and reaction intermediates for methane activation are identical for the $\text{O}$ and $\text{P}$ isomeric forms of the catalytic complex. Both $\text{TS}_\text{oxo}$ and $\text{TS}_1$ exhibit a broken O–O bond, which implies that for catalysts that prefer the $\text{P}$ geometry, $\text{P} \rightarrow \text{O}$ isomerization occurs prior to CH activation. While the isomerization step is supported by a recent computational study, experimental studies are divided between simultaneous O–O cleavage with CH activation and spectroscopic evidence pointing to the formation of a reactive O from P. Owing to the structural and energetic similarity of the O and P TS and intermediate geometries, the reaction pathways and subsequent analysis are referenced to the O isomer. The geometries and bond distances are reported in Figure 1 and Table 3, respectively. Although we calculate a TS for the radical pathway that has an unbroken O–O bond and therefore resembles the P isomer, the electronic energy is 88 kJ/mol higher than $\text{TS}_1$ with a cleaved O–O bond. Therefore, the P-like TS is excluded from subsequent analysis.

Reaction pathways corresponding to the oxo-insertion and radical recombination mechanisms for the O isomer are shown in Figure 2a and Figure 2b, respectively. In both cases, the rate-limiting step corresponds to activation of the CH bond, in agreement with most computational studies of $\text{Cu}_2\text{O}_2$ complexes except those that employ mixed Cu oxidation states.

#### 3.1 Oxo-insertion

The oxo-insertion pathway in Figure 2a was originally proposed in order to explain the retention of configuration observed in pMMO enzyme kinetics experiments. In this mechanism, methanol is formed in a single step, with the TS consisting of simultaneous Cu–O and C–H cleavage and C–O and O–H bond formation. The formation of a methanol product is confirmed with IRC calculations. $\text{TS}_\text{oxo}$ consists of a bent C–H–O configuration (110°) and is associated with an apparent barrier of 90 kJ/mol. Natural bond orbital (NBO) analysis reveals that the difference in the total natural charge on $\text{CH}_4$ between $\text{TS}_\text{oxo}$ and IS is positive (+0.65). This is consistent with experimental observations with aromatic substrates, where the substitution of electron-donating groups stabilizes the positively charged TS and consequently yields higher reaction rates.

The closed-shell singlet catalyst is 68 kJ/mol more stable than the triplet. Both singlet and triplet complexes exhibit weak binding to methane (IS). Although the singlet and triplet TSs are structurally distinct, with greater CH stretch in the former (Table 3), the difference in their energies is very small as a consequence of spin correction. In the absence of spin correction, BS energy

<table>
<thead>
<tr>
<th>Group</th>
<th>Amines N-donor</th>
<th>Imidazoles N-donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCH$_3$</td>
<td>$\text{NH}_2$–O–CH$_3$</td>
<td>![Image](138x655 to 188x666)</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>$\text{NH}_2$–CH$_3$</td>
<td>![Image](142x498 to 184x522)</td>
</tr>
<tr>
<td>H</td>
<td>$\text{NH}_3$</td>
<td>![Image](144x542 to 182x553)</td>
</tr>
<tr>
<td>CF$_3$</td>
<td>$\text{NH}_2$–CF$_3$</td>
<td>![Image](223x492 to 267x527)</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>$\text{NH}_2$–N=O</td>
<td>![Image](225x530 to 266x655)</td>
</tr>
</tbody>
</table>

*Table 2* N-donors which replace all 4 NH$_3$ ligands in the $[\text{Cu}_2(\text{NH}_3)_4\text{O}_2]^{2+}$ catalyst to create complexes with ligands of varying electron-donating or withdrawing character.$^{58}$ The atoms colored blue represent Cu-bound N.
of the triplet state is about 24 kJ/mol higher than the BS energy of the singlet state. While the energetic proximity of the singlet and triplet potential energy surfaces opens up the possibility of spin crossing between the two surfaces (or two-state reactivity), this phenomenon will not have notable kinetic implications since the barriers are very similar.

### 3.2 Radical recombination

The two-step pathway, shown in Figure 2b, consists of a rate-limiting step involving CH cleavage to form radical species, and a recombination step to produce methanol. Singlet TS1 consists of a nearly linear C−H−O configuration (170°). The CH stretch is shorter in TS1 than TSoxo, indicating an early TS for the radical pathway. NBO analysis also confirms the early character of TS1. The charge on the substrate CH₃ is +0.18, which is significantly lower than TSoxo. In the singlet potential energy surface, the nascent CH₃ radical tends to coordinate with Cu, and in the triplet, it is positioned vertically above the oxygen atom. Although IRC calculations sometimes converge to intermediates (INT) that involve ligand coordination of CH₂, there is no evidence of formation of a radical, this study is limited to the calculation of a radical intermediate.

We address some key differences between the TSs calculated here and a recent study by Da Silva et al. using a model pMMO complex in which [Cu₂(O₂)]²⁻ is coordinated to histidine residues. The radical TS reported in their study is characterized by a bent C−H−O configuration (170°). The CH stretch is shorter in TS1 than TSoxo, indicating an early TS for the radical pathway. NBO analysis also confirms the early character of TS1. The charge on the substrate CH₃ is +0.18, which is significantly lower than TSoxo. In the singlet potential energy surface, the nascent CH₃ radical tends to coordinate with Cu, and in the triplet, it is positioned vertically above the oxygen atom. Although IRC calculations sometimes converge to intermediates (INT) that involve ligand coordination of CH₂, there is no evidence of formation of a radical, this study is limited to the calculation of a radical intermediate.

This discrepancy highlights the importance and necessity of IRC analysis, which enables us to verify that calculated TSs indeed correspond to the intended reactant and product molecules.

Based on a comparison of the singlet barriers alone, the oxo-insertion mechanism is energetically favorable compared to radical recombination. However, in agreement with previous studies, triplet TS1 is significantly lower in energy compared to the singlet. In the event that spin-crossover from the singlet to triplet becomes feasible the radical pathway is preferred over oxo-insertion. Therefore, it is evident that the question of preferred CH activation mechanism is not resolved by pathway estimation alone.

### 3.3 Activation Strain Model

Preference for the oxo-insertion pathway in the singlet state is contradictory to prior quantum QM/MM studies by Shiotome and Yoshizawa. They report a higher barrier for the oxo-insertion pathway, which they attribute to the large deformation or strain energy associated with greater CH stretch in TSoxo compared to TS1. The calculated CH distance in TSoxo (Table 3) is similar to the QM/MM study in spite of differences in the choice of ligands and level of theory. However, CH strain alone is insufficient to explain differences in barriers.

We invoke the activation strain model, which states that the activation barrier (ΔEᵢ) is determined by a summation of the strain energy (ΔEstrain), required to deform the IS into the TS, and the interaction energy (ΔEINT) between the fragments constituting the transition state. In this study, the model can be expressed as

\[
\Delta E_i^A = \Delta E_{\text{strain},i} + \Delta E_{\text{INT},i}, \quad i = \text{TSoxo, TS1}
\]

where ΔE stands for the energy difference between TS and IS. The interaction energy differences for the [Cu₂(O₂)]²⁻ system are calculated using EDA. \(\Delta E_{\text{INT},\text{TSoxo}}\) is -54 kJ/mol, which is 93 kJ/mol more favorable than \(\Delta E_{\text{INT},\text{TS1}}\) (+39 kJ/mol). When subtracted from the symmetry-broken electronic energy differences between the transition and initial states (\(\Delta E_{\text{TSoxo}}^A = 144 \text{ kJ/mol}, \Delta E_{\text{TS1}}^A = 230 \text{ kJ/mol}\)), the strain energy associated with TSoxo

<table>
<thead>
<tr>
<th>Spin, Label</th>
<th>Bond length (Å)</th>
<th>Angle(°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS</td>
<td>Cu₁−Cu₂, O₁−O₂, Cu₁−O₂, Cu₁−O₃, Cu₂−O₂, Cu₂−O₃, Cu−N, O₁−H, C−H, C−O₁, C−H−O₁</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>2.697, 2.253, 1.756, 1.756, 1.759, 1.759, 1.937, 2.949, 1.095, 3.746, 129.8</td>
<td></td>
</tr>
<tr>
<td>TSoxo</td>
<td>2.905, 2.295, 1.962, 1.750, 1.967, 1.750, 1.794, 1.794, 1.974, 1.794, 1.974, 1.974, 1.974, 1.974</td>
<td></td>
</tr>
<tr>
<td>TS1</td>
<td>2.832, 2.383, 1.749, 1.760, 2.151, 1.767, 1.947, 1.382, 1.291, 2.663, 170.3</td>
<td></td>
</tr>
<tr>
<td>TS2</td>
<td>3.015, 2.401, 1.874, 1.748, 2.407, 1.787, 1.985, 0.978, 2.404, 1.915, 49.28</td>
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</tr>
<tr>
<td>INT</td>
<td>2.833, 2.369, 1.829, 1.748, 1.987, 1.847, 1.977, 0.989, 2.015, 2.992, 169.2</td>
<td></td>
</tr>
<tr>
<td>FS</td>
<td>2.378, 3.084, 2.250, 1.716, 3.572, 1.707, 1.967, 0.967, 1.961, 1.435, 44.2</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>2.794, 2.313, 1.817, 1.815, 1.812, 1.811, 1.967, 2.514, 1.098, 3.370, 133.9</td>
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</tr>
<tr>
<td>TSoxo</td>
<td>3.046, 2.191, 1.975, 1.796, 1.980, 1.794, 1.997, 1.146, 1.295, 2.261, 135.6</td>
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</tr>
<tr>
<td>TS1</td>
<td>2.829, 2.363, 1.819, 1.735, 1.988, 1.847, 1.975, 1.298, 1.253, 2.549, 176.0</td>
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<tr>
<td>TS2</td>
<td>2.820, 2.431, 1.873, 1.745, 2.058, 1.819, 1.986, 0.972, 2.405, 2.452, 81.2</td>
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<tr>
<td>INT</td>
<td>2.828, 2.374, 1.822, 1.738, 1.987, 1.849, 1.974, 0.987, 2.022, 2.996, 168.7</td>
<td></td>
</tr>
<tr>
<td>FS</td>
<td>3.497, 2.871, 2.022, 1.804, 4.153, 1.717, 2.000, 0.966, 1.984, 1.444, 43.4</td>
<td></td>
</tr>
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</table>
is about 7 kJ/mol higher than TS1. Therefore, the lower barrier for oxo-insertion is a consequence of stabilizing electronic interactions between the methane and catalyst fragments at TSoxo. The increase in strain from TS1 to TSoxo is also not very large in spite of greater CH stretch in the latter. This may be explained by the fact that, in singlet TS1, the nascent CH₃ radical perturbs the ligand field of the nearest Cu atom. This leads to out-of-plane bending of one of the NH₃ groups coordinated to Cu (Figure 1). This deformation is absent in TSoxo. Therefore, the TSs possess similar total strain energies due to a combination of these factors. We note that, in spite of several attempts, we are unable to isolate a singlet TS1 structure that does not involve out-of-plane bending of the N-donor.

The stark difference between ΔE_{INT,TSoxo} and ΔE_{INT,TS1} for the [Cu₂(NH₃)₄O₂]²⁺ system indicates that TS stabilization in each pathway is governed by different types of electronic interactions.

Therefore, EDA is employed to not only break down ΔE_{int} into its constituents, but also analyze trends across catalysts with various N-donors.

### 4 Ligand Effects

The differences in EDA components between the TSs (TSoxo, TS1) and ISs for all the catalysts examined in this study are reported in Table 4. The barriers (labeled E_{TS} - E_{IS}) for oxo-insertion correspond to the BS electronic energy difference between TSoxo and IS in the absence of zero-point corrections. The barriers to the radical formation step correspond to differences using spin-corrected TS1 energies. Spin-correction is not implemented for the oxo-insertion pathway since the extent of contamination from higher spin states (characterized by < S² >) is comparable across all systems. Along similar lines to the parent [Cu₂(NH₃)₄O₂]²⁺ system, total interaction energy differences, ΔE_{INT}, in Table 4 are negative for oxo-insertion and positive for the radical recombination mechanism for all systems.

Frozen interactions (ΔE_{FRZ}), dominated by Pauli repulsions, are repulsive in nature and relatively invariant across all systems for a given reaction pathway. This is largely by design.
because all calculations are carried out by retaining the parent \([\text{Cu}_2(\text{NH}_3)_4\text{O}_2]^{2+}\) active center geometry. Therefore, further breakdown of the frozen interactions into electrostatics, Pauli repulsion, and dispersion interactions is not reported in Table 4. Freezing the active center geometry also implies that, within the activation strain framework, the geometric strain contribution to the barrier is kept constant, allowing us to isolate and analyze purely electronic interactions between the substrate and catalyst. This assumption of negligible variations in strain effects is reasonable because, in spite of geometric constraints during optimization, vibrational analysis shows that TS geometries and energies are sufficiently close to the true TSs.

Favorable fragment orbital relaxations, or mixing of the highest occupied and lowest unoccupied molecular orbitals within a fragment lead to negative polarization energy differences. Owing to the partially charged nature of the fragments determined from NBO, the magnitude of polarization energies are higher in TS\(_{\text{soxo}}\) than TS\(_1\). Similarly, charge transfer contributions are higher for oxo-insertion compared to radical recombination. The larger magnitude of frozen interaction differences in oxo-insertion relative to radical recombination (Table 4) can also be explained using charge transfer. Significant overlap between fragments is essential for favorable charge transfer energies. However, the close proximity of fragment orbitals due to large overlap leads to nearly equal, and repulsive frozen contributions to the interaction energy.\(^{66}\)

The analysis of barrier response to N-donors using EDA components is carried out by referencing the differences in EDA energies (TS-IS) to the parent \([\text{Cu}_2(\text{NH}_3)_4\text{O}_2]^{2+}\):

\[
\Delta \Delta E_k = (E_{k,i} - E_{k,IS}) - (E_{k,i} - E_{k,IS})|_{\text{NH}_3,\text{reference}}
\]

where \(k\) is the total interaction energy or its constituents (INT, FRZ, POL, CT) and \(i\) corresponds to the TS (TS\(_{\text{soxo}}\), TS\(_1\)).

### 4.1 Amine N-Donors

Figure 3 shows the sensitivity of oxo-insertion and radical recombination barriers to variations in amine N-donor electrophilicity, quantified in terms of \(\Delta \Delta E_k\), the EDA components referenced to \([\text{Cu}_2(\text{NH}_3)_4\text{O}_2]^{2+}\). Oxo-insertion barriers are highly sensitive to ligand philicity, ranging from 179 kJ/mol for electron-donating NH\(_2\)CH\(_3\) to 97 kJ/mol for electron-withdrawing NH\(_2\)NO\(_2\) donors. This trend is in agreement with experiments that vary the philicity of the substrate.\(^{16,31,32}\) As described earlier, frozen interactions are relatively insensitive by design. Polarization contributions become more favorable as ligands become more electron-donating. A weak, linear correlation is determined between polarization energy and barrier (\(R^2_{\text{POL}} = 0.72\)). The range of observed differences in \(\Delta \Delta E_{\text{POL}}\), however, is narrow compared to charge transfer. A strong linear relationship exists between charge transfer interactions and barriers to oxo-insertion (\(R^2_{\text{CT}} = 0.95\)), which also translates to linear correlation with the total interaction energy (\(R^2_{\text{INT}} = 0.98\)). In stark contrast to the oxo-insertion mechanism, the barriers to the CH activation step in the radical recombination pathway are invariant to N-donor changes, and lie between 230 and 240 kJ/mol, a range too narrow to analyze variations in a meaningful manner. The insensitivity to N-donor philicity is also

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Ligand type</th>
<th>Ligand</th>
<th>(\Delta \Delta E_{\text{FRZ}})</th>
<th>(\Delta \Delta E_{\text{POL}})</th>
<th>(\Delta \Delta E_{\text{CT}})</th>
<th>(\Delta \Delta E_{\text{INT}})</th>
<th>(E_{\text{TS-IS}})</th>
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reflected in the negligible variations in EDA components and total interaction energies across these systems.

4.2 Imidazole N-Donors

Barrier sensitivity to imidazole N-donors for the oxo-insertion and radical recombination pathways are shown in Figure 4. Similar to amine N-donors, the oxo-insertion barriers are lower for electron-withdrawing substituents in the imidazole donors, although the barriers span a narrower range – 175 kJ/mol for CH$_3$-substituted and 142 kJ/mol for NO$_2$-substituted imidazole N-donors. Polarization energy differences vary very little (< 10 kJ/mol) and no significant trend is observed ($R^2_{POL} = 0.54$). Much like amine N-donors, oxo-insertion barriers are linearly dependent on total interaction energies ($R^2_{INT} = 0.94$), with dominant contributions from charge transfer ($R^2_{CT} = 0.93$). Radical barriers for imidazole N-donors, along similar lines to the amine systems, show little variation with ligand philicity with the minor exception of NO$_2$-substituted imidazole systems, for which the barrier is about 10 kJ/mol lower than the others.

Therefore, we demonstrate that while charge transfer interactions play a dominant role in TSoxo stabilization and rate enhancement by electron-withdrawing ligands, substrate-catalyst interactions in TS1 and radical pathways show negligible dependence on N-donor philicity.

4.3 Hammett Analysis

Figure 5 shows the Hammett plots for the oxo-insertion pathway using $\sigma_m$, $\sigma_p$, and $\sigma_p^+$ Hammett parameters. In each plot, the $\sigma$ values in the x-axis are multiplied by 4 (denoted by $\Sigma$) to account for the number of ligand substitutions.71 Owing to the absence of ligand dependence, poor linear fits ($R^2<0.5$) are obtained for the radical pathway. Therefore, Hammett plots for the radical pathway are not reported.

Irrespective of the choice of $\sigma$ in Figure 5, the $\rho$ values determined for amines as well as imidazoles are negative, and consistent with an electrophilic attack on the substrate.16 In general, the linear fits for amine donors are poorer than imidazole. The linear fits for both sets of donors are also better in the case of $\sigma_m$ and $\sigma_p$ compared to $\sigma_p^+$. Stronger barrier response to amine N-donors yields a $\rho$ value of larger magnitude compared to imidazole N-donors. The three amine $\rho$ values (-5.47, -3.38, -2.03) are therefore not in agreement with experimental reference (-1.48). On the other hand, the range of calculated imidazole $\rho$ values (-3.42, -2.29, -1.45) encompass the experimentally observed slope (-2.2),32 an exact match is obtained with the slope corresponding to $\sigma_p$. The imidazole slopes are also in good agreement with other studies that employ ethylenediamine derivatives as N-donors.16,31 Therefore, the combined evidence obtained from barrier responses and Hammett relationships strongly suggests that oxo-insertion is the preferred pathway for CH activation.

5 Discussion

Although the dioxo-dicopper core is of immense scientific interest owing to its prevalence in CH oxidation enzymes and both homogeneous and heterogeneous catalysts, the reaction mechanism is not well-understood. Along similar lines to previous computational studies,23,24,26 we show that contrasting singlet and triplet potential energy surfaces for the proposed oxo-insertion and radical recombination mechanisms does not entirely resolve the question. The singlet oxo-insertion pathway is energetically more favorable than the singlet radical pathway. A preliminary analysis of solvent effects (ESI) with MeTHF shows that this is still the case even though the oxo-insertion barrier increases by 28 kJ/mol while the radical barrier is unchanged. However, the low barrier to triplet TS1 opens up the possibility of an otherwise prohibitive radical pathway, which involves crossing between the two potential energy surfaces.28,78,79 A quantitatively accurate picture of reaction pathways for multiple spin states is difficult to achieve using DFT. However, the question of appropriateness of a single-reference method (DFT) is at least partially resolved. Since we show that the $P \to O$ isomerization step must precede CH activation,31,33 the entire kinetics study can be referenced to closed-shell, single-reference O isomers without loss of mechanistic information.

Furthermore, focus is shifted from improving barrier accuracies to probing oxo-insertion and radical barrier responses to perturbations in the catalyst, and quantifying the electronic interactions that govern these responses. Inspired by experimental studies16,31,32 which demonstrate that electron-donating groups coordinated to the substrate lead to higher reaction rates, the electrophilicity of N-donors in the catalyst are systematically varied. Although several post-DFT analysis methods81–83 are available to quantitatively probe electronic or orbital interactions between the catalyst and substrate, energy decomposition analysis is chosen since it is a natural fit with the activation strain framework that separates strain from electronic effects. This choice is also inspired by a computational study, which uses EDA, and specifically its charge transfer components, to estimate and utilize philicity to classify CH metal-insertion catalysts.84

The analysis of ligand-dependence using DFT and EDA yields interesting results. As seen in Figures 3 and 4, distinct trends emerge for singlet oxo-insertion and radical recombination pathways. Frozen interactions for either pathway are invariant to N-donor changes by design. In the oxo-insertion pathway, polarization, or intrafragment relaxation, is more favorable when ligands are more electron-donating. This is because the partial positive charge on the CH$_4$ fragment in TSoxo is favorably polarized by electron-donating groups in the catalyst fragment. However, polarization contributions to TSoxo stabilization are much smaller than charge transfer or interfragment relaxation. Overlap between substrate and catalyst orbitals becomes more favorable with electron-withdrawing N-donors since they enhance the electrophilic character of the [Cu$_2$O$_2$]$^{2+}$ active center. Trends in TSoxo total interaction energies mirror charge transfer energies. Commensurate with the activation strain framework in which strain is invariant, a linear relationship exists between total interaction energies and oxo-insertion barriers. Decrease in barriers is sharper with amine donors than imidazole N-donors. We hypothesize that this is a consequence of greater proximity of amine donors to the active center through direct bonding (“inductive effect”) to the Cu-coordinated N atom. In complete contrast
Fig. 3 EDA with amine N-donors referenced to [Cu$_2$(NH$_3$)$_4$O$_2$]$^{2+}$: (a) Oxo-insertion and (b) Radical recombination barrier dependence on frozen (top, left), polarization (bottom, left), charge transfer (top, right), and total interaction energies (bottom, right). Data labels correspond to the ligands described in Table 2. Solid lines correspond to linear fits and the corresponding $R^2$ value of the fit is reported in the bottom right corner for the oxo-insertion pathway.

to oxo-insertion, by virtue of possessing an early TS with only a small CH stretch relative to CH$_4$, the radical pathway is far less sensitive to variations in N-donors in the catalyst. Therefore, no observable changes in substrate-catalyst interactions or barriers are reported. However, weak resonance stabilization may account for small barrier lowering achieved in the case of NO$_2$-substituted imidazole seen in Figure 4(b).

The range of observed oxo-insertion barriers via catalyst perturbations is significantly wider than those observed in experiments which vary the ligands bonded to the substrate. In spite of these differences in barriers as well as choice of N-donors and substrates across experiments, mechanistic comparisons are possible through the calculation of slopes ($\rho$) of Hammett plots, shown in Figure 5. Due to the absence of N-donor dependence, the radical pathway exhibits no discernible trends, in direct contrast to experiments which typically report a small negative $\rho$ around -2.2. Therefore, it is unlikely that a singlet radical pathway is observed in experiments.

Poor linear fits ($R^2 \leq 0.81$) are obtained for oxo-insertion with amine donors, possibly due to the fact that a Hammett parameter, by definition, is not an appropriate descriptor for non-aromatic substitutions. Calculated $\rho$ values are much more negative than the chosen experimental reference (-1.48). However, this is in line with the preceding EDA study, which shows more extensive charge delocalization with amine donors than imidazole, that translates to a more negative slope in the Hammett plot.

We observe excellent agreement between $\rho$ values for the oxo-insertion pathway with imidazole donors, particularly between $\sigma_p$, and experiments. This is surprising for two reasons – (1) a linear relationship and matching slope are obtained in spite of the unconventional use of the Hammett parameter for N-donor substitutions, (2) the slope is relatively agnostic to whether the substrate is a phenolate, benzyl, or, in our case, an aliphatic system, and whether each Cu atom is coordinated to 2 (DFT) or 3 (experiment) N-donors. The computational Hammett study therefore corroborates experimental observations of electrophilic substitution, and the combined evidence strongly points towards oxo-insertion as the preferred pathway for CH activation, independent of whether the CH bond belongs to an aliphatic or aromatic substrate. Based on the agreement in $\rho$ values and the TSoxo structure, we can also conclude that the rate-limiting step consists of simultaneous C−H and Cu−O cleavage and O−H and C−O formation. In other words, the rate-limiting step does not also involve simultaneous O−O cleavage for dicopper kinetics starting from the P isomer.

Our approach combines DFT-based mechanistic calculations with a systematic analysis of ligand effects on both substrate-catalyst interactions as well as reaction rates. The trends obtained from both EDA and Hammett analysis for singlet oxo-insertion are in good agreement with experiment. The study also shows that, due to multiple ligand substitutions, stronger rate trends are observed with modifications to the catalyst rather than the substrate. To obtain a more direct comparison with experiments, therefore, we propose the design of complementary experimental and computational studies to probe CH activation mechanisms through catalyst substitutions and using a substrate with weaker CH bonds than CH$_4$. A potential issue we foresee with experimental design is associated with obtaining rates that are experimentally measurable (reactions that are neither too fast nor too slow). Consequently, it is difficult to predict whether the range of barriers obtained for experimentally measurable reaction rates are large enough to be resolved using computations. However,
Fig. 4 EDA with imidazole N-donors referenced to \([\text{Cu}_2(\text{NH}_3)_4\text{O}_2]^{2+}\): (a) Oxo-insertion and (b) Radical recombination barrier dependence on frozen (top, left), polarization (bottom, left), charge transfer (top, right), and total interaction energies (bottom, right). Data labels correspond to the ligands described in Table 2. Solid lines correspond to linear fits and the corresponding \(R^2\) value of the fit is reported in the bottom right corner for the oxo-insertion pathway.

Our calculations show stark trends—strong ligand-dependence is observed for one proposed mechanism and is completely absent in the other, irrespective of the type of N-donors. We conclude, therefore, that the design of complementary experiments and computations for dioxo-dicopper complexes must be feasible.

We also identify some limitations of the computational approach. While the combined experimental and computational evidence points towards an oxo-insertion pathway, we have not rigorously eliminated the possibility of radical spin-crossing. For the radical pathway, it can be argued that the minimum energy crossing point (MECP), located energetically closer to the triplet than the singlet, is more appropriate than singlet TS1 for calculating barrier responses. However, based on the small CH stretch observed in both singlet and triplet TS1, the MECP is expected to be structurally similar, and therefore also an early TS which exhibits low sensitivity to changes in N-donors. Although we partially sidestep some of the common accuracy issues associated with density functional approximations for transition metal complexes and spin states by contrasting trends rather than absolute energies, it is possible that these errors are not entirely eliminated. It is also possible that these trends are influenced by solvation and relativistic corrections, which are not taken into account in this study. Steric effects are negligible in these systems due to the small sizes of N-donors, which allows us to simplify barrier response analysis by neglecting frozen interactions. To make the approach truly generalizable to N-donors of any size and shape, frozen interactions and their constituents will become an important part of EDA-based barrier response analysis. In addition to affecting frozen interactions, it is possible that steric effects play a more direct role in the mechanism. Since the proximity of the substrate to the catalyst is greater in TSoxo than TS1, the presence of bulky groups in the substrate or catalyst either renders the catalyst inactive or necessitates the exploration of alternate mechanisms for CH activation. Our objective, going forward, is to examine the relative importance of the effects outlined above, and develop a more detailed picture of CH activation in these catalysts.

6 Conclusions

This study utilizes density functional approximations with model dicopper complexes and \(\text{CH}_4\) to calculate potential energy surfaces for oxo-insertion and radical recombination, two proposed pathways for CH activation. Transition states and reaction intermediates for pathways starting with the P and O isomer are identical, indicating that P→O isomerization occurs prior to CH activation. While the singlet oxo-insertion barrier is lower than the singlet radical barrier, the triplet radical pathway, via spin-crossing, may offer a lower energy route to CH activation. Rather than probing the possibility of spin-crossing, we examine the sensitivities of both mechanisms to systematic variations in the electrophilicity of catalyst N-donors. While the singlet oxo-insertion barrier is considerably lowered upon enhancing the electron-withdrawing character of N-donors, the radical barrier is relatively constant. This is because the former possesses a partially charged TS that is stabilized via charge transfer interactions with the catalyst, while the latter possesses a very early radical-like TS with a small CH stretch that is far less sensitive to changes in N-donors. Within the activation strain framework, the oxo-insertion barrier is considerably lowered upon enhancing the electron-withdrawing character of N-donors, the radical barrier is relatively constant. This is because the former possesses a partially charged TS that is stabilized via charge transfer interactions with the catalyst, while the latter possesses a very early radical-like TS with a small CH stretch that is far less sensitive to changes in N-donors. Within the activation strain framework, the oxo-insertion barriers vary linearly with EDA-based total interaction energies. The oxo-insertion barriers for various N-donors are then used to derive Hammett relationships. Calculated slopes (\(\rho\)) of Hammett plots for imidazole donors are consistent with an electrophilic
Fig. 5 Hammett plots for the oxo-insertion pathway with amine ($T = 193K$) and imidazole ($T = 148K$) substituents using (a) $\sigma_m$: Hammett parameter for meta-substituted benzoic acid, (b) $\sigma_p$: Hammett parameter for para-substitution, and (c) $\sigma^*_p$: corrected Hammett parameter for para-substitution.\textsuperscript{72} The summation ($\Sigma$) accounts for the fact that 4 substitutions are made in each catalyst. The $R^2$ value and slopes ($\rho$) of the linear fits are reported.

mechanism and also in quantitative agreement with experiments. Taken together, we have preliminary evidence to suggest that one-step oxo-insertion is the preferred pathway for CH oxidation in dioxo-dicopper complexes.

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8 Conflicts of interest
There are no conflicts of interest to declare.

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