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Understanding and Breaking Scaling Relations in Single-Site Catalysis: Methane-to-methanol Conversion by Fe(IV)=O

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ABSTRACT: Computational high-throughput screening is an essential tool for catalyst design, limited primarily by the efficiency with which accurate predictions can be made. In bulk heterogeneous catalysis, linear free energy relationships (LFERs) have been extensively developed to relate elementary step activation energies, and thus overall catalytic activity, back to the adsorption energies of key intermediates, dramatically reducing the computational cost of screening. The applicability of these LFERs to single-site catalysts remains unclear, owing to the directional, covalent metal-ligand bonds and the broader chemical space of accessible ligand scaffolds. Through a computational screen of nearly 500 model Fe(II) complexes for CH₄ hydroxylation, we observe that 1) tuning ligand field strength yields LFERs by comparably shifting energetics of the metal 3d levels that govern stability of different intermediates and 2) distortion of the metal coordination geometry breaks these LFERs by increasing the splitting between the d_{xz}/d_{yz} and d_z^2 metal states that govern reactivity. Thus, in single site catalysts, low Brønsted-Evans-Polanyi slopes for oxo formation, which would limit peak turnover frequency achievable through ligand field tuning alone, can be overcome through structural distortions achievable in experimentally characterized compounds. Observations from this screen also motivate the placement of strong HB donors in targeted positions as a scaffold-agnostic strategy for further activity improvement. More generally, our findings motivate broader variation of coordination geometries in reactivity studies with single-site catalysts.

Keywords: density functional theory, single-site catalysis, high-throughput screening, catalyst design, minimal models, linear scaling relations, methane activation, iron-oxo

1. Introduction

The selective partial oxidation of methane to methanol is a critical challenge¹ that would unlock widespread use of natural gas as a chemical feedstock². At present, the only commercially viable chemical use of methane is through steam reforming to CO and H₂, an energy- and capital-intensive process³. The direct transformation of methane to methanol is particularly challenging due to the high bond dissociation energy (BDE) of the C-H bond together with the thermodynamic favorability of over-oxidation to CO₂, thus motivating an exhaustive search for selective and active yet stable catalysts⁴⁻⁹.

Thanks both to advances in method development and available computational power, first-principles computational catalysis¹⁰⁻¹¹ has made major contributions towards the design of improved catalysts by providing a molecular-scale understanding of catalytic action¹²⁻¹⁷ and enabling screening of candidate materials faster than can be readily achieved in an experimental setting¹⁸⁻²². For high-throughput computational screening²³⁻²⁶, it becomes advantageous to reduce the computational cost of assessing catalytic activity by relating it to efficiently computed descriptors, rather than explicitly computing activation energies of all elementary steps for each catalyst candidate²⁷. In this regard, heterogeneous catalyst screening extensively leverages linear free energy relationships (LFERs), i.e., linear scaling relations between intermediates²⁸⁻³⁰ and Brønsted-Evans-Polanyi (BEP) relations³¹⁻³² between activation and reaction energies, to predict reactivity trends and relate overall catalytic activity to the energies of key intermediates^{26, 33-35}. Such linear scaling relations are valid not only for the flat surfaces for which they were originally formulated²⁸, but also for other commonly employed catalyst structures such as nanoparticles³⁶⁻³⁸, stepped and kinked sites³⁷, and bifunctional materials³⁹⁻⁴⁰. In many of these structures, changes in LFER slopes and intercepts have been successfully rationalized and captured in predictive

models^{37, 39} that broaden the scope of materials that can be efficiently screened when aiming to identify materials at the top of the “volcano” maximum in activity.

Known limitations of LFERs in heterogeneous catalysis should cast doubt on their straightforward application to single-site transition metal (TM) catalysts where bonding is highly variable. Simple models such as the *d*-band model⁴¹⁻⁴³ satisfactorily rationalize the slope of linear scaling relations in bulk metals but are known to be insufficient for metal-organic bonding in crystalline materials⁴⁴⁻⁴⁵ and may not adequately capture the directional, covalent metal-ligand bonds in TM complexes⁴⁶. Indeed, even the most straightforward bulk metal scaling relations can be disrupted by the introduction of *p*-block impurities⁴⁷. Most studies on LFERs in single-site catalysts have focused on electrochemical reactions such as reduction of O₂⁴⁸⁻⁵¹, CO₂⁵² and N₂⁵³ due to the strong parallels between single-site and surface mechanisms^{33, 54-55} as well as the typically valid assumption that redox rather than chemical steps are rate-limiting. Among these studies, linear scaling relations have been observed across variations in metal and ligand connecting atom identity within a fixed scaffold⁵³, but the covalency of metal-reactive-moiety bonds has also resulted in slopes that do not agree with bond order conservation⁵⁰.

Within chemical catalysis, it remains unclear the extent to which LFERs will be preserved or disrupted across the broad ranges of accessible single-site catalyst ligand scaffolds. An improved understanding would benefit the discovery of single-site C-H activation catalysts, which is of significant interest^{19-21, 23} owing to higher achievable activities and selectivities than their surface counterparts⁵⁶. Inspiration for single-site methane to methanol catalyst development comes from native enzymes (e.g., methane monooxygenase) that efficiently convert methane to methanol under mild conditions through Fe(IV)-oxo intermediates⁵⁷. Indeed, model biomimetic complexes have been synthesized that hydroxylate larger alkanes under similar conditions⁵⁸⁻⁵⁹. However,

discovery of stable and active single-site catalysts for this challenging reaction will necessitate screening across a wide design space, which can be accelerated by an LFER-based approach. Across the subsets of complexes where LFERs hold, thermodynamic properties of key intermediates can be employed to accelerate screening in analogy to computational heterogeneous catalysis or by relating activity to experimental quantities (e.g., acidity constants⁶⁰⁻⁶¹, hydricities⁶²⁻⁶³ and redox potentials⁶⁴⁻⁶⁶).

Another concern unique to single-site catalysis is that one can introduce through-space noncovalent interactions (NCIs) such as proximal hydrogen bond (HB) donors⁴⁸⁻⁴⁹ and distal positively charged groups⁵². These NCIs can interact distinctly with differing intermediates, thus affecting linear scaling relations by decoupling the relative adsorption energies of intermediates^{29-30, 33-34, 67-68}. Although it is known that proximal HB donors stabilize the oxo moiety in synthetic Fe(IV)-oxo complexes that hydroxylate alkanes⁶⁹⁻⁷¹, their effect on the overall catalytic cycle, and hence the feasibility of targeted NCI design as a strategy to improve catalytic activity for C-H activation, is less well-established.

In this work, we advance understanding of LFERs in single-site chemical catalysis through a systematic computational screen of nearly 500 equilibrium and distorted model Fe(II) complexes for methane hydroxylation. We demonstrate for the first time that scaffold distortion not only breaks strong linear scaling relations arising from ligand field strength tuning but also alters BEP relations for oxo formation. We clarify the role of relative energies of individual *3d* orbitals in mediating these phenomena and explore how distortion may be accessed in stable complexes to potentially improve existing catalysts. We also examine the possibility of further activity improvements through targeted design of NCIs. The rest of this manuscript is as follows. In section 2, we provide details of our screening approach and the calculations employed in this

work. In section 3, we present Results and Discussion on the effects of metal electronic structure and NCIs on LFERs. Finally, in section 4, we provide our Conclusions.

2a. Reaction Mechanism and Screening Approach

The mechanism of catalytic partial oxidation of light alkanes to alcohols by mononuclear non-heme Fe centers using N₂O as the terminal oxidant is well established¹⁶. It involves 1) the formation of an Fe(IV)-oxo moiety that abstracts a hydrogen atom from the substrate alkane (i.e., CH₄ in this work or C₂H₆ in experiments⁷²), 2) a rebound hydroxylation step yielding Fe(II)-CH₃OH, and 3) methanol product release to regenerate the resting Fe(II) catalyst (Figure 1, left). Relative to hydrogen atom transfer (HAT, **3** → **4**), oxo formation (**2** → **3**) occurs with a high barrier^{16, 72}, typically making it the turnover-determining transition state (TDTS)²¹. The rebound step (**4** → **5**) is strongly exothermic and nearly barrierless¹⁶ such that the turnover-determining intermediate is always Fe(II)-CH₃OH (**5**) (Figure 1, right). We characterize the energetic landscape of the catalyst in terms of the energy changes of oxo formation (ΔE_1), HAT (ΔE_2), and CH₃OH release (ΔE_3) (Figure 1, right):

$$\Delta E_1 = E(\mathbf{3}) - E(\mathbf{1}) - \frac{1}{2}E(\text{O}_2) \quad (1)$$

$$\Delta E_2 = E(\mathbf{4a}) + E(\text{CH}_3\cdot) - E(\mathbf{3}) - E(\text{CH}_4) \quad (2)$$

$$\Delta E_3 = E(\mathbf{1}) + E(\text{CH}_3\text{OH}) - E(\mathbf{5}) \quad (3)$$

To further simplify the screening process, we omit the antiferromagnetically coupled CH₃• from **4** because its contribution to reaction energies is nearly constant across catalyst complexes studied (**4a** in Figure 1 and Supporting Information Figure S1). In order to maximize generality of computed trends beyond N₂O as the terminal oxidant, we have also omitted N₂O-containing species (i.e., **2**) from our reaction energy screen in favor of the oxo formation energy (ΔE_1), which is the BDE of the Fe=O bond in **3** with respect to a triplet O₂ reference. Alternative

references, e.g., H_2O , singlet O or anionic O^{2-} , will shift computed energies by a constant factor without affecting trends⁷³, and N_2O is incorporated explicitly when calculating activation energies (Sec. 3b).

Figure 1. Catalytic cycle for the oxidation of CH_4 to CH_3OH by Fe(II) catalysts. (left) The intermediates for which energies are calculated in Sec. 3a are enclosed in rounded rectangles. (right) A simplified energy level diagram of the reaction energies for three key steps with associated intermediate numbers: oxo formation (ΔE_1), HAT (ΔE_2), and methanol release (ΔE_3).

We curated two distinct sets of complexes to represent accessible bonding motifs in single-site catalysts (Figure 2). **Set 1**, designed to isolate inner-sphere effects, contains a total of 540 tetracoordinate scaffolds built from minimal ligand models with varying connecting atom identities (i.e., N, P, O, or S) and coordination geometries (i.e., metal-ligand distances and metal-ligand plane dihedral angles, referred to simply as the dihedral angle) (Figure 2, top). The N, O, P, and S elements were selected as connecting atoms because they commonly occur in natural and synthetic first-row transition metal complexes, and we generated complexes by saturating coordinating atoms alternately with hydrogen or methyl groups. The four ligand connecting atoms are constrained to be planar, and the metal atom is distorted out of the plane (i.e., metal-ligand Fe-3L dihedral angles of 10, 20, and 30°), producing an overall square pyramidal geometry. In order to mimic ligand field effect differences in extended scaffolds that can

influence metal-ligand bond lengths, metal-ligand bonds were both stretched and compressed from designated equilibrium values for a total of 3 bond lengths per complex. The list of dihedral angles and connecting-atom-specific metal-ligand distances considered, together with the parameters constrained during geometry optimizations, is provided in Supporting Information Tables S1-S2. This approach, previously demonstrated for the design of closed-shell Zn carbonic anhydrase mimics⁷⁴, leverages the locality of transition metal chemistry⁷⁵⁻⁷⁶ to reproduce the primary variations in metal electronic environments possible with the vast space of synthetically accessible metal-organic scaffolds at a reasonable computational cost, as demonstrated in Sec. 3c. Overall, these geometric and connecting atom variations produce a total of 540 catalyst models when both homoleptic and heteroleptic combinations are considered (i.e., $\text{Fe(II)}(\text{L}^1)_2(\text{L}^2)_2$ where L^1 and L^2 are allowed to differ, see Figure 2).

Set 1:

Minimal models

36 ligand combinations

5 Fe-L distances

3 Fe-3L dihedrals

Total of 540 scaffolds

Set 2:

Functionalized N4Py

2a: $\text{R}^1 = \text{FG}$

2b: $\text{R}^3 = \text{FG}$

2c: $\text{R}^1 = \text{R}^4 = \text{FG}$

2d: $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{FG}$

40 functionalized scaffolds

Figure 2. Construction of **Set 1** (minimal models, top) and **Set 2** (functionalized N4Py, bottom). All structures carry a +2 net charge. In **Set 2**, unfunctionalized attachment points are occupied by hydrogen atoms.

Set 2, designed to isolate second-sphere effects, consists of 40 functionalizations of the pentadentate N4Py (*N,N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine) scaffold⁷⁷ constructed from a pool of 10 functional groups (FGs) and 4 attachment points on the pyridine rings closest to the metal active site (Figure 2, bottom). Despite its relatively large size (49 atoms), N4Py is an ideal choice for isolating second-sphere effects because its rigidity ensures that the FGs remain proximal to the active site. The asymmetry in the attachment points to the central iron-reactive moiety site also enables investigation of distance dependence of NCIs within a single scaffold. The FGs in the pool contain only one heavy atom of varying size, electronegativity, and valence, and are expected to interact with moieties bound to the active site through electrostatic (e.g., with halides), steric, and hydrogen bonding (e.g., with OH or NH₂) effects (Figure 2).

2b. Computational Details

First-principles calculations. Energetics of reaction steps were calculated as differences of total electronic energies. All single-point energy calculations, frequency calculations, and geometry optimizations were performed with a development version of the TeraChem⁷⁸⁻⁷⁹ graphical processing unit (GPU)-accelerated quantum chemistry package, using density functional theory (DFT) with the B3LYP⁸⁰⁻⁸² global hybrid functional augmented with the empirical DFT-D3 correction⁸³ (i.e., B3LYP-D3). The default definition of B3LYP in TeraChem employs the VWN1-RPA form for the LDA VWN⁸⁴ component of LYP⁸¹ correlation, and the default D3 correction used includes Becke-Johnson damping⁸⁵. This selection was motivated by the fact that although DFT-calculated reaction energies in TM complexes are strongly functional-dependent⁸⁶⁻⁸⁸, relative energetics between catalyst variants are more invariant to functional

choice (Supporting Information Figure S2). All calculations were spin-unrestricted and use the composite LACVP* basis set, which consists of the LANL2DZ effective core potential⁸⁹⁻⁹⁰ for Fe, Br, and I and the 6-31G* basis set for all other atoms.

Our modest basis set size, chosen to accelerate screening in a large compound space, is justified as trends in relative energies are not strongly sensitive to basis set choice (Supporting Information Figure S3). All calculations were performed in the gas phase, and inclusion of implicit solvent effects did not alter computed trends (Supporting Information Figure S4). Basis set superposition error (BSSE) corrections were neglected after the magnitude of BSSE was determined to be independent of the complexes being compared (Supporting Information Figure S3). Zero point vibrational energy and entropic contributions as computed under the harmonic approximation were neglected due to negligible effect on computed trends (Supporting Information Figure S5).

All intermediates were simulated with a net charge of +2, as all ligand scaffolds studied are neutral and no counterions were included. The latter choice was motivated by the high ionization potentials of light alkanes (here, CH₄) relative to heavier counterparts that is known to prevent unphysical charge delocalization⁹¹⁻⁹². To decouple spin-splitting energies from the underlying energetic trends, all intermediates were simulated in the high-spin state (sextet for **4a** and quintet otherwise). However, as the triplet spin surface is generally less reactive than the quintet spin surface as a result of exchange-enhanced reactivity⁹³⁻⁹⁴, a negative triplet-quintet spin-state splitting⁹⁵⁻⁹⁶ would be a concern for catalyst design.

Structures. Geometry optimizations used the L-BFGS algorithm in translation rotation internal coordinates (TRIC)⁹⁷ as implemented in a development version of TeraChem⁷⁸⁻⁷⁹ to the default tolerances of 4.5×10^{-4} hartree/bohr for the maximum gradient and 1×10^{-6} hartree for the

change in self consistent field (SCF) energy between steps. Initial guess geometries for resting catalyst complexes were generated with the molSimplify⁹⁸ toolkit, employing custom bond lengths for minimal models and the custom core feature for functionalized scaffolds. Proceeding across the catalytic cycle, guess geometries for intermediates and transition states (TSs) were generated by automatically functionalizing and distorting earlier optimized structures using custom routines to be included in a future release of molSimplify. Constrained geometry optimizations were employed for **Set 1** to maintain the desired ligand coordination geometry, whereas unconstrained geometry optimizations were used for **Set 2** (see Supporting Information Table S2 for details). A list of all complexes studied in this work and their optimized geometries are provided in the Supporting Information Tables S1-S2 and attached coordinate files. Of the 540 minimal model scaffolds in **Set 1**, 135 were discarded because of covalent bonding of the oxo moiety in the Fe(IV)-oxo intermediate with a ligand connecting atom upon geometry optimization. Of the 40 substituted scaffolds in **Set 2**, 3 were discarded due to covalent bonding of the oxo moiety in the Fe(IV)-oxo intermediate with the heavy atom on the FG (Supporting Information Table S1).

For selected minimal model complexes in **Set 1** (Sec. 3b), approximate TSs were obtained with the nudged elastic band (NEB) method with climbing image⁹⁹⁻¹⁰⁰ as implemented in DL-FIND¹⁰¹, also at the B3LYP-D3/LACVP* level of theory. These searches were performed in Cartesian coordinates with metal and ligand atoms frozen at their reacting-complex coordinates. For revised complexes in **Set 1** (Sec. 3b), exact TSs were instead obtained with partitioned rational function optimization (P-RFO)¹⁰² at the B3LYP-D3/LACVP* level of theory using QChem 4.4¹⁰³ and were characterized with vibrational frequency analysis to confirm a single imaginary frequency. TeraChem single-point energy calculations on the resulting structures

obtained from QChem were obtained to enable direct energy comparisons between intermediates and TSs because Hessian-based TS optimization is not available in TeraChem.

Cambridge Structural Database (CSD)¹⁰⁴ searches were performed using the ConQuest 1.19 program¹⁰⁵ with constraints on metal and connecting atom identity, basic three-dimensional connectivity and torsion angles analogous to those specified in constrained geometry optimizations. Hits were manually filtered to separate fully coordinated complexes from unsaturated complexes with counterions completing the coordination sphere, and DFT optimizations were performed on selected structures in the quintet state after removing counterions to ensure preservation of the desired coordination environment. The ConQuest search files used are provided in the Supporting Information.

3. Results and Discussion

3a. Inner-Sphere Tuning

We begin by correlating ΔE_1 , ΔE_2 and ΔE_3 across the over 400 structures in **Set 1** to explore whether metal-ligand (i.e., inner-sphere) tuning of single-site catalysts yields linear scaling relations. The variations in computed reaction step energies are large across all three steps: from -15 to 30 kcal/mol for oxo formation (ΔE_1), -20 to 20 kcal/mol for HAT (ΔE_2), and 20 to 65 kcal/mol for CH₃OH release (ΔE_3) (Supporting Information Figure S6). These variations confirm that inner-sphere tuning in this minimal ligand model set strongly affects the energetic landscape (Figure 3 and Supporting Information Figure S6). Across all variations in dihedral, bond length, and ligand connecting atom identity in **Set 1**, we observe weak to moderate linear scaling relations among ΔE_1 , ΔE_2 , and ΔE_3 (Figure 3). After exclusion of a single outlier (see Sec. 3c), moderate negative correlations are observed between oxo formation and HAT (ΔE_1 vs. ΔE_2 , $R^2 = 0.52$) and between HAT and methanol release (ΔE_2 vs. ΔE_3 , $R^2 = 0.59$) (Supporting Information

Figure S7). We observe a weaker positive correlation between oxo formation and methanol release (ΔE_1 vs. ΔE_3 , $R^2 = 0.26$) (Supporting Information Figure S7). Qualitatively, these relationships emphasize that making typically turnover determining oxo formation more favorable could make HAT so unfavorable that it becomes turnover determining instead.

In comparison, stronger linear scaling relations have been observed in heterogeneous systems with varying metal identity, oxidation state, and coordination number (e.g., $R^2 = 0.88$ for metal oxides¹⁰⁶, and a mean absolute error of 3.0 kcal/mol across a broad range of oxo-supporting heterogeneous motifs³⁵ vs. 3.4 kcal/mol in this work). Thus, even with the fixed metal identity, oxidation state, and coordination number we have employed, the limits for linear scaling relations as predictive tools in single-site catalysis are apparent. However, the increased tunability of metal coordination environments in single-site catalysts relative to their heterogeneous counterparts suggests we should be able to identify and control the source of scatter to increase or shift the peak of previously known volcano relationships^{21,35}.

Upon closer inspection, correlations between oxo formation and HAT ΔE_1 and ΔE_2 appear to group by the metal-ligand plane dihedral angle (Figure 3). Thus our minimal models enable systematic isolation of an effect previously observed on tuning HAT energetics in multidentate catalyst scaffolds that induce metal-ligand plane distortion²⁰. Indeed, restricting correlations to complexes with the same dihedral angle greatly improves linear fits ($R^2 = 0.88$ to 0.92) while keeping the scaling-relation slope almost unchanged (-0.60 to -0.66) (Supporting Information Figure S8). As the dihedral angle increases, both ΔE_1 and ΔE_2 decrease by approximately 1.2 and 3.7 kcal/mol(10°) respectively, which tends to favor the turnover-determining step regardless of whether oxo formation or HAT is turnover determining (Supporting Information Table S4).

Within fixed metal-ligand plane dihedral scaling relations, variations in ligand identity determine energetic relationships. Along a given dihedral scaling relation, oxo formation is favored and HAT is disfavored (i.e., more exothermic ΔE_1 and more endothermic ΔE_2) for 1) P or S connecting atoms (i.e., $S \approx P > O > N$), 2) methylated ligand connecting atoms, and 3) compressed metal-ligand bond lengths. To test whether functionalization beyond two atoms from the metal center affects energetics, we substituted the hydrogen atoms on the methyl groups of representative ligands and confirmed that these distant changes have little effect⁷⁶ (Supporting Information Table S3). The dominant effects are additive: the structures in **Set 1** with the most exothermic ΔE_1 contain a strong ligand field and charge donation^{20, 107-108} to the metal afforded by methylated, compressed P and S ligands. The benefit of minimal models for discovery of reactivity dependence on inner-sphere properties at reduced computational cost is evident from the wide range of energetics spanned.

Figure 3. Oxo formation energy (ΔE_1 , in kcal/mol) versus HAT energy (ΔE_2 , in kcal/mol) for minimal model complexes in **Set 1**. The minimal models are grouped by metal-ligand plane dihedral angle: 10° (circles), 20° (triangles), and 30° (squares). Symbols are colored according to the corresponding CH_3OH release energy (ΔE_3 , in kcal/mol), as indicated in the inset color bar. A single outlier is indicated by a red border.

The effect of dihedral angles on linear scaling relations can be rationalized by qualitative molecular orbital (MO) analysis⁴⁶ of the metal d orbitals available to overlap with ligand valence orbitals. On the quintet spin surface, exchange-enhanced reactivity⁹³⁻⁹⁴ should favor the $^5\sigma$ HAT

pathway, in which an electron is added to the σ^* lowest unoccupied MO (LUMO) of Fe(IV)-oxo with majority d_z^2 character (Figure 4). In accordance with expectations from frontier MO theory¹⁰⁹, the Fe(IV)-oxo LUMO eigenvalue is a good descriptor for ΔE_2 ^{20-21, 107} (Supporting Information Figure S9). Oxo formation (ΔE_1) is instead governed by the eigenvalues of the d_{xz} , d_{yz} and d_z^2 orbitals oriented for binding the axial oxo moiety. For constant dihedral angle, ligand field strength tuning that modulates charge donation to the metal^{120, 107-108}, e.g., through changes in metal-ligand bond length or ligand connecting atom, shifts these d states equivalently (Figure 4, right). This constant effect on multiple d states, in analogy to cases in the solid state where the d -band center shifts but the d -band width is unchanged,⁴¹⁻⁴³ explains the stronger linear scaling relations observed in recent work in bulk metals and MOF cluster models.^{21, 35} Increasing the dihedral angle presents an opportunity to break these strong linear scaling relations (i.e., simultaneously decreasing ΔE_1 and ΔE_2) by stabilizing the d_z^2 LUMO while simultaneously destabilizing the d_{xz} and d_{yz} orbitals (Figure 4, left). These effects of structural distortion on the eigenvalues of metal d -states may be rationalized in terms of variations in ligand-orbital overlap¹¹⁰, and representative DFT-calculated eigenvalues support this qualitative picture (Supporting Information Table S5).

Figure 4. Qualitative illustration of how increasing the dihedral angle (left and schematic, top left) and weakening the ligand field strength (e.g., by stretching the metal-ligand bonds) (right and schematic, top right) tunes the relative energetics of d -states on the quintet surface.

Molecular orbitals are labeled according to their primary atomic orbital character.

In CH₃OH release, the positive, albeit weak, correlation between ΔE_1 and ΔE_3 , suggests inner-sphere tuning that favors oxo formation should also favor product release for a synergistic effect on catalytic activity (Figure 3). Examining complexes in which oxo formation is relatively favorable confirms that they also have relatively low CH₃OH binding energies (Figure 3, top left). However, for cases where oxo formation is highly favorable, HAT energetics can instead control activity. In this case, the stronger, negative correlation between HAT and CH₃OH release (i.e., ΔE_2 vs. ΔE_3) will stabilize bound methanol and limit the benefit of inner-sphere tuning. This behavior nominally violates the expectation that the binding energies of ligands with the same connecting atom should be positively correlated^{28, 53}, likely due to the very different character and strengths of the iron-oxo and iron-methanol interactions. In methanol binding, as in water binding¹¹¹, charge is transferred from the O lone pairs to the vacant d_z^2 orbital in an analogous manner to HAT, rationalizing the stronger correlation of CH₃OH release with HAT than with oxo formation. Unlike scaling relationships between HAT and oxo formation, no further improvement is improved in linear scaling relationships between HAT and CH₃OH release for constant dihedral angle or connecting atom identity (Supporting Information Figure S10). These weak correlations highlight the potential of single-site catalyst motifs to disrupt or broaden known scaling relations between intermediates. However, the limited benefit of linear scaling relations will require alternative approaches, such as the minimal models employed here, to efficiently reveal energetic trends over wide regions of chemical space.

3b. Activation Energies

We next investigate the validity of BEP relations for HAT and oxo formation to confirm that our thermodynamic trends also hold for activation energies. We model oxo formation as oxygen

atom transfer from N₂O (Figure 1). We define activation energies for the oxo formation ($E_{a,O}$) and HAT ($E_{a,H}$) reaction steps as follows:

$$E_{a,O} = E(\text{TS1}) - E(\text{2}) \quad (4)$$

$$E_{a,H} = E(\text{TS2}) - E(\text{3}) - E(\text{CH}_4) \quad (5)$$

We will quantify the applicability of BEP relations between these activation energies and reaction energies that explicitly include the intermediates omitted in Sec. 3a:

$$\Delta E_O = E(\text{3}) + E(\text{N}_2) - E(\text{2}) \quad (6)$$

$$\Delta E_H = E(\text{4}) - E(\text{3}) - E(\text{CH}_4) \quad (7)$$

We first select a 43 complex homoleptic subset of **Set 1** that still includes the primary effects of i) dihedral angle, ii) direct connecting atom variations (i.e., N, O, P, or S), iii) ligand methylation vs. hydrogen termination, and iv) metal-ligand bond length elongation and compression (Supporting Information Table S6). Over this representative subset, we observe a strong BEP relation for HAT between $E_{a,H}$ and ΔE_H ($R^2=0.99$), with a slope of 0.97 (Figure 5, top). In some cases, $E_{a,H}$ is negative because it is defined relative to infinitely separated reactants. The quality of fit is independent of dihedral angle or connecting atom identity, confirming that a general BEP relation holds for HAT among our minimal models, and that the conclusions derived from thermodynamic analysis (Sec. 3a) remain valid when the HAT barrier is explicitly considered. Although good correlations have been noted in previous HAT studies^{35, 112-114}, the very high correlation coefficient here is uniquely attributable to the combination of 1) a consistent ⁵σ HAT mechanism and substrate identity and 2) involvement of only metal-substrate interactions.

Since the strong HAT relationship stands out among the other weaker correlations we have

identified in single-site catalysts, it is useful to quantitatively probe its origin. For instance, the high correlation in the HAT BEP could be due to similarity of the TS and the product structure regardless of catalyst identity. To quantify early or late TS character in HAT, we use the difference between the cleaving C-H and forming O-H bond lengths in the TS (Δd) as a metric, normalized by a value of 0.861 Å that represents the largest difference among HAT product complexes in our dataset:

$$\Delta d = \frac{d_{\text{C-H}}^{\text{TS}} - d_{\text{O-H}}^{\text{TS}}}{0.861} \quad (8)$$

A negative value denotes an earlier TS, a positive value denotes a later TS, and a value of 1 corresponds to an infinitely late (i.e., product complex) TS. Computed Δd values range from somewhat early (-0.18) to late (0.31). These TSs obey the Hammond postulate¹¹⁵ i.e., more endothermic reactions have later TSs. Energy decomposition along the reaction coordinate¹¹⁶⁻¹¹⁷ for representative early and late TSs reveals equivalent strain in substrates but earlier and larger contributions to stabilization for early TSs (Supporting Information Figures S11-S12). The close-to-unity BEP slope is thus unusual because it does not result from very late TSs, as it does in surface-catalyzed methane hydroxylation¹¹⁵, but rather from a close relationship between what causes TS stabilization and what makes the reaction step more favorable.

Figure 5. Activation energy ($E_{a,H}$ and $E_{a,O}$, kcal/mol) vs. reaction energy (ΔE_H and ΔE_O , kcal/mol) for the HAT (top) and oxo formation (bottom) reaction steps. Gray diamonds indicate fully relaxed octahedral complexes, and the minimal models are grouped by metal-ligand plane dihedral angle: 10° (blue circles), 20° (green triangles) and 30° (red squares). A single best-fit line has been obtained through both 20° and 30° data.

To study oxo formation BEP relations, we now select a 76 complex homoleptic subset of **Set 1** that includes the primary effects of i) dihedral angle, ii) direct connecting atom variations (i.e., N, O, P, or S), iii) ligand methylation vs. hydrogen termination, and iv) metal-ligand bond length elongation and compression (Supporting Information Table S7). Both the HAT and oxo formation subsets were drawn from the same pool of homoleptic complexes, but the oxo formation subset is larger because it contains structures that were removed from the HAT subset due to difficulty in locating a HAT TS (Supporting Information Tables S6-S7). Over this subset, we observe a weaker overall relationship between $E_{a,O}$ and ΔE_O in oxo formation ($R^2=0.62$) along

with a lower slope of 0.34 (Figure 5, bottom). The oxo formation reaction step energy, ΔE_o , can exceed $E_{a,o}$ because ΔE_o is defined relative to infinitely separated products. As previously observed for linear scaling relations, restricting correlations to groups with low (10°) or high (20 - 30°) dihedral angles improves correlation coefficients (to $R^2=0.77$ - 0.81 , see Figure 5). As the dihedral angle is increased, the intercept decreases by 4-5 kcal/mol up to a 20° dihedral value, but the slope remains nearly unchanged (Figure 5, bottom). Analysis of TS geometries reveals these distinct BEP relationships to be due to decreasing Fe-O distance relative to the O-N distance as the dihedral angle is increased (Supporting Information Figure S13). This suggests that greater changes to oxo formation barriers can be achieved through structural distortion than through ligand field tuning of reaction thermodynamics, highlighting a limit to conventional BEP relations for molecular catalysis. Such an observation is particularly surprising given the strong BEP relation observed for HAT with the same catalysts.

Examination of the electronic structure changes accompanying oxo formation on the quintet surface explains the unusual dependence on dihedral angle in oxo formation BEP relations. We have identified that the oxo formation energy depends on d_{xz}/d_{yz} and d_z^2 stability. However, the two-electron transfer from Fe(II) to the incipient N_2 is apparently sequential despite a single TS along the reaction coordinate: the lower-energy d_{xz}/d_{yz} is transferred early and the higher-energy d_z^2 later, as confirmed by localized orbital analysis¹¹⁸⁻¹²⁰ (schematic in Figure 6 and visualized natural orbitals shown in Supporting Information Figure S14). This sequential electron transfer has not been previously noted in C-H activation catalyst design screens but was observed in an analogous reverse reaction, the sulfoxidation of thioanisole by Fe(IV)-oxo¹²¹. Oxo formation E_a and ΔE_r are thus partially decoupled because the TS energy is more strongly dependent on d_{xz}/d_{yz} stability than the reaction energy. Decreasing the energy difference between the d_{xz}/d_{yz} and d_z^2

orbitals, e.g., by distorting the metal out of the plane of the ligands, should decrease E_a relative to ΔE_r by preferentially favoring the first electron transfer leading to the TS.

Figure 6. Schematic of electronic structure changes accompanying oxo formation. The red circles indicate the order of electron transfer along the reaction coordinate, and spectator orbitals (d_{xy} and $d_{x^2-y^2}$) are shaded in gray.

To further explore the extent of strong oxo formation BEP relations, we created a new 22 complex subset derived from **Set 1** variations in which we added axial ligands to enable full TS characterization. Over 14 complexes, we added a water distal axial ligand while varying i) ligand connecting atom (N, O, and S), ii) ligand methylation, and iii) included both heteroleptic and homoleptic combinations; in 8 additional complexes, we held the equatorial ligands fixed (i.e., homoleptic NH_3) and varied the distal axial ligand widely (Supporting Information Table S8). Relative to constrained minimal models, we observe an expected upward shift of the BEP trendline for this 22 molecule subset because the distal axial ligand in a monodentate structure will favor near-zero metal-ligand dihedral angles (Figure 5, bottom). We also expected limited dependence of this effect on nature of the distal axial ligand because changing distal axial ligand field strength will shift d_{xz}/d_{yz} and d_z^2 comparably. Indeed, over this revised subset, we observe a comparable slope with higher intercept of 35.8 kcal/mol (Figure 5). The larger variation ($R^2=0.50$) is likely attributable to variations in now-unconstrained metal-ligand bond lengths in

the TS (Figure 5 and Supporting Information Table S9).

Coupled with linear scaling relations, the BEP slopes in undistorted complexes suggest that ligand field tuning will increase the HAT barrier by ~ 3 kcal/mol for every 1 kcal/mol decrease in the oxo formation barrier. For catalyst design, these observations present a challenge: although increasing ligand field strength, as has been recently considered in computational modeling of MOFs²¹, should lower an oxo formation TDTS, it may make HAT the TDTS. Our observations on distorted structures suggest a complementary approach to improve catalytic activity beyond ligand field tuning alone. To explore how distorted metal-ligand angles may be accessed in stable complexes, we searched the CSD¹⁰⁴ for undercoordinated Fe(II) complexes with a tetracoordinate equatorial ligand scaffold supporting a large dihedral angle (see Sec. 2b for details). Among these macrocyclic complexes, large dihedrals are found in complexes with relatively small rings, e.g., 24° in a 12-membered cyclam ring (CSD: QIJLEC¹²²) and 20° in a porphyrinogen (CSD: YEXVED¹²³) (Figure 7, top). Tetrapodal ligands can also promote out-of-plane distortion of the metal atom by anchoring the equatorial ligands to the axial ligand, although dihedrals are typically lower than in macrocyclic complexes (Figure 7, bottom). Examples of such motifs include the prototypical N4Py (CSD: FAZHOE⁷⁷, 14° dihedral) or an analogous, carboxylate-rich scaffold (CSD: SARRUA¹²⁴, 15° dihedral). In addition to energetics, stability may also be a concern when selecting one of these choices for dihedral distortion: probable ligand redox non-innocence¹²³ in the porphyrinogen likely limits its application in C-H activation.

Figure 7. Representative four-coordinate (top) and five-coordinate (bottom) Fe(II) complexes with large metal-ligand plane dihedral angles obtained from a CSD search. The structures are labeled with their CSD accession code and largest DFT-optimized dihedral angle.

3c. Second-sphere Effects

We now explore how catalytic activity can also be modulated by second-sphere (i.e., proximal to the metal center but non-bonding) effects over the 37 structures in **Set 2** (details in Sec. 2). First, we verify that properties from larger scaffolds at equilibrium can be mapped onto our minimal model structure-energy relationships. The unfunctionalized N4Py scaffold has a metal-ligand plane dihedral angle of 14° and strong ligand field arising from sp^2 N-coordinating equatorial ligands and axial σ -donating NR_3 moiety, meaning it should have similar energetic relationships to strong field minimal models with moderate metal-ligand plane dihedrals. Indeed, N4Py energetics are close to strong field (i.e., compressed PMe_3 and SMe_2) minimal models with 10 - 20° dihedrals (Figure 8, red circle and Supporting Information Figure S15). This agreement of N4Py with the minimal models validates their use to efficiently reveal variations in energetic relationships in single-site catalysis. Nevertheless, second-sphere functionalizations of N4Py in

Set 2 produce distinct behavior that cannot be achieved with inner-sphere tuning alone: oxo formation energetics are affected most strongly (ΔE_1 , 30 kcal/mol range), methanol release less so (ΔE_3 , 20 kcal/mol range), and HAT is almost unchanged (ΔE_2 , 5 kcal/mol range) (Figure 8 and Supporting Information Figure S16).

Figure 8. Oxo formation energy (ΔE_1 , in kcal/mol) versus HAT energy (ΔE_2 , in kcal/mol) for **Set 2** (unfunctionalized N4Py shown as a red circle). The corresponding data points from **Set 1** minimal model complexes are represented as translucent circles. The functionalizations are colored according to the corresponding CH_3OH release energy (ΔE_3 , in kcal/mol), as shown in color bar at right.

To confirm that the addition of FGs do not have an inner-sphere, electronic effect (e.g., through change of electron density at the metal), we constructed isomers with FGs oriented away from the metal center. In all cases, we recovered comparable energetics to the unfunctionalized N4Py, validating this tuning strategy as orthogonal to inner-sphere tuning and originating solely from non-covalent interactions (NCIs) between the second-sphere FGs and bound moieties (Supporting Information Table S10). As a result, scaling relations derived from the electronic structure of the metal center cannot apply here, providing an orthogonal energetic tuning strategy that is expected to be feasible on any scaffold that can enable positioning of FGs within appropriate distances to reacting species.

Examination of individual points in **Set 2** confirms qualitative expectations of putative FG-bound moiety interactions. Given limited variation of HAT energetics (i.e., ΔE_2), we first focus

on ΔE_1 and ΔE_3 and subtract the unfunctionalized N4Py energy differences to isolate the effect of second-sphere FGs:

$$\Delta\Delta E_r = \Delta E_r - \Delta E_r(\text{N4Py}) \quad (9)$$

where r is 1 or 3. A negative value of $\Delta\Delta E_1$ thus corresponds to a reduction in ΔE_1 upon functionalization and relative stabilization of the oxo moiety, and a negative value of $\Delta\Delta E_3$ corresponds to a reduction in ΔE_3 and increased favorability of methanol release (i.e., destabilization of the bound methanol). We classify each **Set 2** functionalized scaffold by its dominant NCI: I) pure steric repulsion from heavy atoms with low electronegativity (i.e., $-\text{CH}_3$, $-\text{SiH}_3$, $-\text{PH}_2$ and $-\text{SH}_2$), II) electrostatic repulsion by electronegative heavy atoms with no bonded H atoms (i.e., $-\text{F}$, $-\text{Cl}$, $-\text{Br}$ and $-\text{I}$), and III) HB stabilization from HB donors^{69-71, 125-126} (i.e., $-\text{NH}_2$ and $-\text{OH}$). These qualitative groupings of NCI types are readily corroborated by electronic structure analysis of the $\text{Fe}=\text{O}$ bond in the oxo moieties (Supporting Information Table S11).

We observe strong clustering into the three Groups due to divergent effects of the different NCI types (Figure 9). Group I steric repulsion destabilizes both oxo and methanol by an amount that increases with i) the van der Waals radius of the heavy atom ($\text{Si} > \text{S} \approx \text{P} > \text{C}$), ii) the proximity of the FG to the reacting moiety (i.e., $2a > 2b$), and iii) the number of FGs (i.e., $2d > 2c > 2a = 2b$) (see definitions in Figure 2 and Supporting Information Table S12). In most cases, methanol is destabilized less than oxo, suggesting that increased structural flexibility from the weaker Fe-O interaction outweighs any increased steric repulsion from the larger size of methanol (Supporting Information Figure S17). The rigid N4Py scaffold studied here does not allow for low-energy distortion that could mask the effect of steric repulsion in more flexible scaffolds¹²¹. Returning to the outlier observed in minimal model complexes (Figure 3 in Sec. 3a),

the 10 kcal/mol higher oxo formation energy (ΔE_1) than would be predicted from inner-sphere effects alone can now be attributed to expected steric repulsion effects between the oxo moiety and the bulky, compressed NMe₃ ligands (Supporting Information Figure S18). Group II electrostatic repulsion trends are comparable to Group I for oxo destabilization (i.e., positive $\Delta\Delta E_1$). The additional electrostatic nature of the repulsion however stabilizes bound methanol (i.e., increased $\Delta\Delta E_3$) due to the halogen atoms acting as HB acceptors to the hydroxyl on methanol.

Figure 9. Relative CH₃OH release energy ($\Delta\Delta E_3$, in kcal/mol) versus relative oxo formation energy ($\Delta\Delta E_1$, in kcal/mol) for **Set 2** complexes, with respect to values for the unfunctionalized N4Py scaffold. The data points are classified according to the FG interaction type (I: gray, II: red, and III: blue) as well as the number and positions of attached FGs (symbol shape: 2a and 2b are mono-, 2c are di- and 2d is tetra-functionalized, as in Fig. 2). Symbols below the dashed line are expected to improve activity in cases where oxo formation is turnover determining.

Group III HB donors stabilize both oxo and methanol, with oxo stabilized slightly more than methanol, consistent with relative HB acceptor strengths predicted from differences in the electrostatic potential¹²⁷ (Supporting Information Figure S19). One outlier in Group III results from strong hydrogen bonding between FGs when no axial moiety is present (Supporting Information Figure S20). In all cases, the relative insensitivity of ΔE_2 arises from the very

similar size and shape of the oxo and hydroxo moieties. Although the hydroxyl group in methanol can act as a HB donor to FGs in the scaffold, the hydroxo moiety alone is much smaller and cannot form such interactions.

These observations may be applied to formulate guidelines for targeted NCI design to improve catalytic activity. If oxo formation is turnover determining, then the oxo group should be stabilized more than bound methanol or the bound methanol should be destabilized more than the oxo group in order to increase turnover frequencies (i.e., $\Delta\Delta E_3 < -\Delta\Delta E_1$). Several **Set 2** points satisfy this target, and most are in Group III (e.g., N4Py with four hydroxyl groups, see also Supporting Information Table S12). Thus, hydrogen bonding NCIs, often employed to stabilize synthetic Fe(IV)-oxo intermediates^{69-71, 125} and implicated in enzyme catalysis¹²⁸, represent the most promising second-sphere interaction for improving activity. Basic HB donors with high BDEs such as amides^{69, 129-130} should also be used to disfavor reaction with the oxo group via HAT or proton-coupled electron transfer¹¹³.

A potential limitation of the use of HB donors to improve activity is the concomitant stabilization of inactivated Fe(III)-oxo. Owing to its formal Fe-O bond order of 1.5 and significant charge and spin localization on O, Fe(III)-oxo is a stronger HB acceptor than Fe(IV)-oxo^{70, 131}. The reduced iron-oxo can thus act as a low-energy off-cycle intermediate, e.g., through electron transfer from Fe(IV)-oxo (Supporting Information Figure S21). Hence, it is important to ensure that the scaffold contains no easily ionizable groups and to minimize contact between the metal centers of multiple catalyst sites to prevent outer-sphere electron transfer. Additionally, as demonstrated from experimental studies focused on O₂^{70, 132} and peroxide¹²⁹ activation, the effective barrier of routes to Fe(IV)-oxo that require sequential oxidation is higher, but this can be overcome by the use of two-electron oxidants, such as iodosylbenzene or N₂O, or by

electrochemical oxidation.

Taking these factors into account and drawing on previous efforts in HB design for electrochemical ion separation⁶⁸, we expect that iterative scaffold and FG design to facilitate placement of HB donors closer to the oxo group than the methanol group should be a feasible strategy for improving catalytic activity, and such efforts are underway in our group.

4. Conclusions

Through our screen of constrained minimal model Fe(II) scaffolds for CH₄ hydroxylation, we have confirmed that they represent a feasible strategy to identify local reactivity trends at a greatly reduced computational cost while providing insight into the breadth of design space in molecular catalysts. The systematic tuning of coordination environments afforded by this approach also enabled us to identify deviations in linear free energy relationships (LFERs) between the oxo formation and hydrogen atom transfer (HAT) reaction steps that provide a path to overcoming 1D volcano-type activity limitations. In particular, increasing the out-of-plane distortion of the metal center 1) increases thermodynamic favorability of both oxo formation and HAT and 2) preferentially favors the oxo formation TS relative to its products, thus breaking well-known LFERs. Through a qualitative MO analysis, we identified the splitting between the d_{xz}/d_{yz} and d_z^2 orbitals to be the key factor governing not only the existence of oxo formation/HAT linear scaling relations but also the differing strengths of oxo formation and HAT BEP relations. Although pure equatorial or axial ligand field tuning does not affect this gap and yields the LFERs typically observed in heterogeneous analogues, increasing the dihedral angle reduces this gap by simultaneously destabilizing the d_{xz}/d_{yz} orbitals and stabilizing the d_z^2 orbital. As these orbitals are not the highest occupied MO, caution should be used when invoking the HOMO eigenvalue as a reactivity descriptor for open-shell single-site catalysts. We

demonstrated that dihedral angle distortions induced in our minimal model simulations are also present in experimentally characterized transition metal complexes, providing a potential route to improve current alkane hydroxylation catalysts.

As an alternative strategy to direct metal-ligand tuning, we functionalized a rigid, asymmetric N4Py scaffold to examine the range of influence of non-covalent interactions on reaction energetics. Here, we observed divergent effects of steric repulsion, electrostatic repulsion, and hydrogen bonding on the relative energies of each elementary step. These observations suggest that catalyst scaffold design to improve activity should focus on the introduction of strong HB donors to preferentially stabilize the oxo moiety over the hydroxo and methanol moieties.

Overall, our work shows that LFERs can be leveraged in single-site catalyst screening only when the coordination geometry is held fixed. Reliance solely on LFERs for single-site catalysis will thus miss rich areas of chemical space accessible through scaffold distortion. This increased computational cost for screening can be offset by characterization of minimal, representative models that can be characterized at a much lower computational cost than extended systems.

ASSOCIATED CONTENT

Supporting Information. Coordinates of optimized geometries; lists of absolute energies; ConQuest search files; lists of complexes studied; minimal model constrained geometry optimization details; effects of methyl radical, basis set, functional, implicit solvent and ZPVE/entropy on computed trends; additional correlation plots; dihedral angle sensitivities of reaction energies; representative DFT eigenvalues; TS geometry analyses; HAT activation strain analysis; oxo formation localized orbital analysis; distally substituted N4Py scaffold energetics; effects of NCIs on Fe(IV)=O; relative **Set 2** reaction energies; geometric analyses of steric repulsion in **Set 2** and Fig. 3 outlier; electrostatic potential analysis of HB acceptor strengths; illustration of intramolecular HBs in **Set 2**; effect of NCIs on Fe(III)-oxo stability. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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