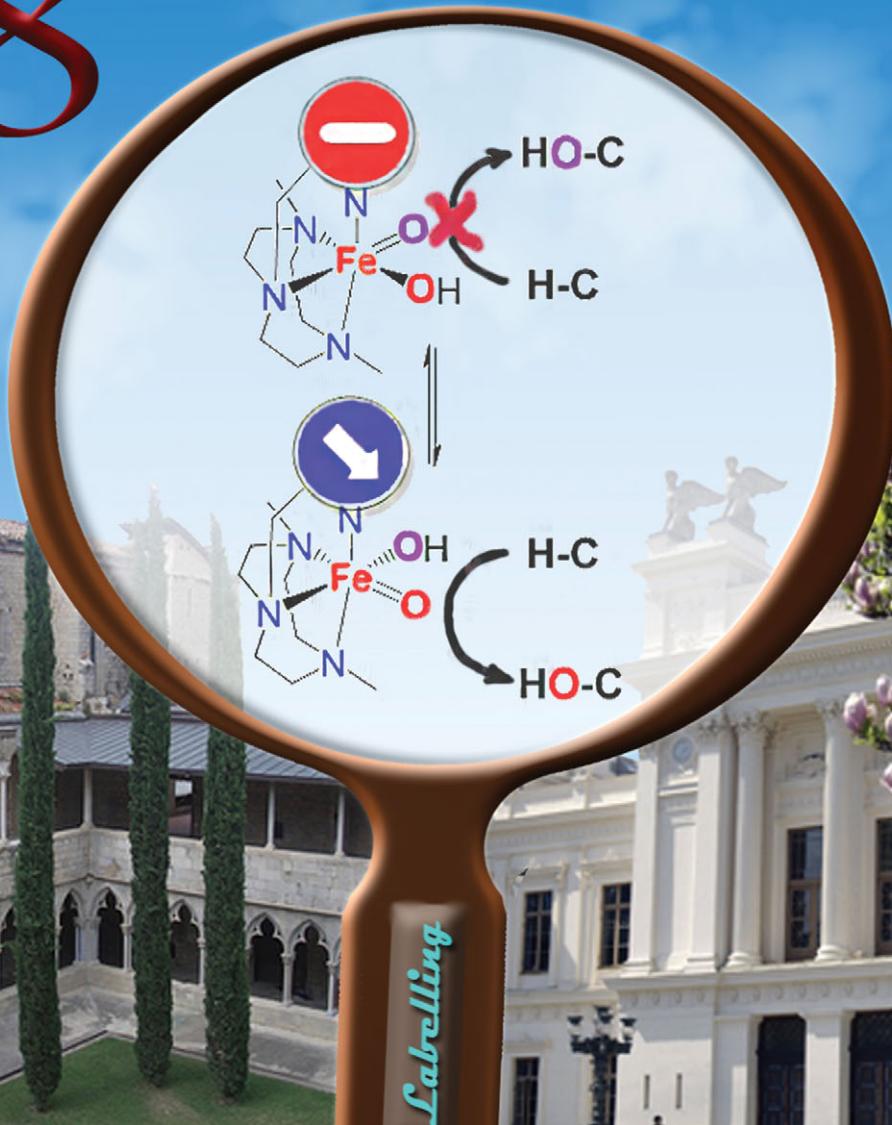


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Evidence that steric factors modulate reactivity of tautomeric iron-oxo species in stereospecific alkane C–H hydroxylation

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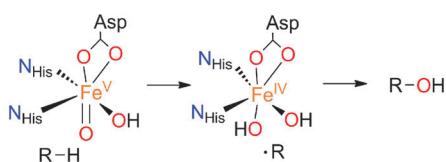
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A new iron complex mediates stereospecific hydroxylation of alkyl C–H bonds with hydrogen peroxide, exhibiting excellent efficiency. Isotope labelling studies provide evidence that the relative reactivity of tautomERICALLY RELATED OXO–IRON SPECIES RESPONSIBLE FOR THE C–H HYDROXYLATION REACTION IS DOMINATED BY STERIC FACTORS.

While the selective functionalization of hydrocarbons remains a significant challenge for chemists,¹ several iron-dependent oxygenases are able to mediate the hydroxylation of C–H bonds under mild conditions, using dioxygen as the terminal oxidant.² Examples include the cytochrome P450 enzymes,³ and the family of non-heme iron-dependent Rieske oxygenases.⁴ In both cases, C–H hydroxylation occurs with almost complete stereoretention, and is accomplished *via* the intermediacy of an electrophilic high valent iron–oxo species that attacks the C–H bond *via* the so-called oxygen-rebound mechanism (Scheme 1).⁵



Scheme 1 Schematic mechanism for C–H hydroxylation by a Rieske oxygenase enzyme.

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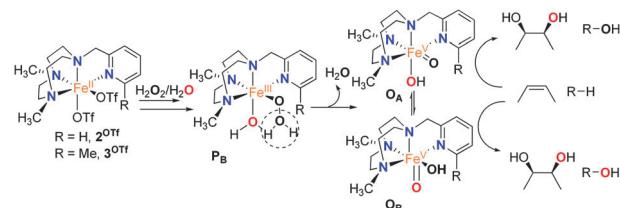
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† Electronic supplementary information (ESI) available: Ligand synthesis, complex synthesis, proton NMR spectra, ESI-MS and IR spectra of the complex, crystallographic data for complexes **1^{OTf}** and **1^{H2O}**, catalysis experiments and results and details of isotope labelling experiments. CCDC 960138 and 960139. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc47830k

A fundamental difference between heme and non-heme sites is that active sites in the latter contain lower coordination numbers, and a number of them form reactive intermediates containing a *cis*-Fe(O)(X) unit (X = HO(H), Cl, Br). This leads to a versatile reactivity that opens new mechanistic scenarios. Arene *cis*-dihydroxylation and aliphatic chlorination constitute unique examples of the reactivity exhibited by *cis*-Fe(O)(X) units (X = OH, Cl and Br).^{4,5b,6}

The reactivity of non-heme oxygenases has inspired the design of synthetic model complexes as selective C–H oxidation catalysts.⁷ Mechanistic studies have shown that in selected cases reactions are metal based, involving high-valent oxo–iron species, and are fundamentally distinct from radical pathway Fenton processes.⁸ The Fe(PyTACN) family of complexes (Scheme 2) belongs to the group of catalysts that mediate C–H hydroxylation with retention of configuration.^{8d} We and others have proposed a mechanistic scenario resembling the “peroxide shunt”³ of cytochrome P450 and model systems. A highly electrophilic [Fe^V(O)(OH)(L^{N4})]²⁺ oxidant (**O**), formed *via* water-assisted cleavage of a hydroperoxide [Fe^{III}(OOH)(OH₂)(L^{N4})]²⁺ (**P_B**) (Scheme 2), is ultimately responsible for C–H oxidation reactions.^{8a,d,9–11} Intermediate **O** can exist as two tautomERICALLY RELATED SPECIES, **O_A** and **O_B**, that differ in the relative positions of the oxo and hydroxide ligands, and are connected through prototypic oxo–hydroxo tautomerism. We have also previously studied C–H oxidation reactions using a set of catalysts where electronic properties of the PyTACN ligand were systematically tuned, and found that the relative reactivity of **O_A** and **O_B** in C–H oxidations remains basically the same, irrespective of the catalyst.^{8d}

In this work we turn our attention towards investigation of steric effects. Towards this end, C–H oxidation reactions catalyzed



Scheme 2 Mechanism for substrate oxidation by Fe(PyTACN) complexes.



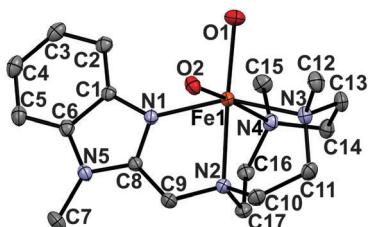


Fig. 1 Molecular structure of $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})_2(\text{Me}_2\text{BzIm}^{\text{+}}\text{TACN})]^{2+}$ ($1^{\text{H}_2\text{O}}$) with 30% probability ellipsoids; H-atoms have been omitted for clarity.

using the new iron complex $[\text{Fe}^{\text{II}}(\text{CF}_3\text{SO}_3)_2(\text{Me}_2\text{BzIm}^{\text{+}}\text{TACN})]$ (Fig. 1), 1^{OTf} , were studied. The new tetradeinate ligand $\text{Me}_2\text{BzIm}^{\text{+}}\text{TACN}$ has been developed by replacing the pyridyl arm of the PyTACN scaffold by an *N*-methyl benzimidazolyl substituent. The sp^2 character and the rigidity of the latter substituent should provide a well-defined steric demand, intermediate between the α -H and the α -Me groups of a pyridine (Scheme 2, catalysts 2^{OTf} and 3^{OTf}). On the other hand, the relative donor capacities of pyridine and benzimidazole can be estimated to be very similar by comparing the $\text{p}K_{\text{a}}$ values of their conjugate acids (5.22 for pyridine, 5.41 for benzimidazole and 5.57 for α -Me pyridine), and therefore differences in reactivity among this set of complexes can be traced to steric factors.

The complexes $[\text{Fe}^{\text{II}}(\text{CF}_3\text{SO}_3)_2(\text{Me}_2\text{BzIm}^{\text{+}}\text{TACN})]$, 1^{OTf} , and $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})_2(\text{Me}_2\text{BzIm}^{\text{+}}\text{TACN})](\text{CF}_3\text{SO}_3)_2$, $1^{\text{H}_2\text{O}}$, were prepared and characterized following standard procedures (see ESI† for details). The X-ray structures of 1^{OTf} and $1^{\text{H}_2\text{O}}$ are very similar to those of 2^{OTf} and 3^{OTf} and have an iron center in a distorted octahedral environment surrounded by the four N atoms of the ligand, with the TACN ring capping one face of the octahedron, and two oxygen atoms of triflate anions (1^{OTf}) or water molecules ($1^{\text{H}_2\text{O}}$) *cis* to each other (cf. Fig. 1 and ESI†).^{8d} Average $\text{Fe}-\text{N}_{\text{TACN}}$ and $\text{Fe}-\text{O}_{\text{H}_2\text{O}}$ distances are 2.23 Å and 2.13 Å respectively, characteristic of a high spin ferrous center.¹²

Complex 1^{OTf} was found to be an outstanding catalyst in C–H oxidation reactions with H_2O_2 . Catalytic oxidation of cyclohexane was chosen for appropriate comparison with literature precedents.^{8,13} Syringe pump addition of 10 equivalents (w.r.t. the complex) of H_2O_2 together with 1000 equivalents of $\text{H}_2\text{O}_2^{\ddagger}$ to a CH_3CN solution containing 1 and a substrate (1000 equivalents) over 30 min in air at room temperature resulted in the formation of cyclohexanol (A) with a turnover number (TON) of 8.5 and a small amount of cyclohexanone (K) with a TON of 0.8, giving an alcohol/ketone (A/K) ratio of 10.6. The efficiency w.r.t. consumption of the oxidant was around 99–100%, and remains unusually high (54%) when 100 equiv. of H_2O_2 are employed. Interestingly, when followed over time, the A/K product ratio in oxidation of cyclohexane showed that the initial value of A/K was around 35, which gradually decreased to 10.6 (cf. Fig. S5, ESI†). This provides strong evidence that cyclohexanol is the almost exclusive primary product of the alkane oxidation reaction, and cyclohexanone is a result of further oxidation of the alcohol, thereby eliminating the significant implication of a Russell-type termination mechanism initiated by hydroxyl radicals and producing equal amounts of alcohol and ketone.

Several mechanistic probes further substantiate that the reactions are metal-based. The intermolecular kinetic isotope effect was determined for the formation of cyclohexanol from a mixture (1:3) of cyclohexane and its deuterated isotopomer cyclohexane- d_{12} , and was found to be 5. Also, complex 1^{OTf} oxidizes adamantane with a large C3/C2 normalized selectivity (14) towards the tertiary C–H bond. The oxidation of *cis*-1,2-dimethylcyclohexane (DMCH) leads to the corresponding tertiary alcohol product with 97% retention of configuration. These data are consistent with the implication of selective oxidants whose relative reactivities against C–H bonds are modulated by their bond strengths and steric properties.^{7a} The reactivity of 1^{OTf} against these mechanistic probes is thus in good accordance with that described for iron catalysts that mediate stereospecific C–H hydroxylation, including those of the $[\text{Fe}(\text{PyTACN})]$ family.^{8d} Since these catalysts operate *via* a $[\text{Fe}^{\text{V}}(\text{O})(\text{OH})(\text{L}^{\text{N}4})]^{2+}$ (O) oxidant,^{8a,d,10,11} the same was tentatively inferred for 1^{OTf} . Strong experimental evidence in favor of this scenario arises from olefin *cis*-dihydroxylation reactions. The water assisted cleavage of the O–O bond (Scheme 2) determines the oxygen atom inventory in the $\text{HO}-\text{Fe}^{\text{V}}=\text{O}$ oxidant (O). One of the oxygen atoms originates from the water molecule, while the second oxygen atom is derived from the peroxide. *cis*-Dihydroxylation reactions incorporate both oxygen atoms of O into the product and consequently *syn*-diols must contain one oxygen atom that originates from water and one oxygen from the peroxide.¹¹ Indeed, 1^{OTf} catalyzes the oxidation of cyclooctene (1^{OTf} : H_2O_2 : H_2^{18}O : cyclooctene, 1:10:1000:1000) affording *cis*-cyclooctene epoxide (TON = 2) and *syn*-cyclooctane-1,2-diol (TON = 7). The *syn*-diol is 98% $^{16}\text{O}^{18}\text{O}$ labeled, providing strong support in favor of O as the oxidant.

Having obtained positive evidence that 1^{OTf} operates through the same mechanism as that of 2^{OTf} and 3^{OTf} , we proceeded to investigate the relative reactivity of the O_A/O_B tautomers in C–H hydroxylation reactions. Since the origin of the oxygen atoms is determined in the peroxide precursor (P_B), the relative reactivity of O_A and O_B in C–H hydroxylation can be probed using isotopically labeled water and hydrogen peroxide (Scheme 2). The oxidation of cyclohexane by 1^{OTf} in the presence of 10 equivalents of $\text{H}_2^{18}\text{O}_2$ and 1000 equivalents of H_2O afforded 45% ^{18}O -labeled cyclohexanol. Complementary experiments with 10 equivalents of H_2O_2 and 1000 equivalents of H_2^{18}O afforded 48% ^{18}O -labeled cyclohexanol (Table 1).

Similar levels of ^{18}O -label incorporation from H_2^{18}O were observed in the case of cyclooctane (41%) and cyclohexane- d_{12} (48%). These levels of water incorporation are unusually high, only bypassed in the literature by 2^{OTf} ,^{8d} and constitute strong evidence that O_A and O_B are roughly equally reactive against secondary C–H bonds. Most interestingly, when the substrates contain tertiary C–H bonds (e.g. DMCH and adamantane), the percentages of ^{18}O incorporation from H_2^{18}O were found to be in the range 25–29%, indicating a preferential oxidation *via* O_A .

Interpretation of these values can be done by considering those obtained using 2^{OTf} and 3^{OTf} in analogous reactions. Table 1 shows that hydroxylation of tertiary C–H bonds mediated by 2^{OTf} is predominantly performed by O_B as shown by the large extent of oxygen atoms originating from water in the alcohol



Table 1 Comparison of percentage of ^{18}O incorporation into alcohol products by different Fe-catalysts using 1000 equivalents of H_2^{18}O

Substrate	1^{OTf}	2^{OTf}	3^{OTf}	Fe(TPA) ^b
Cyclohexane	48	45	11	29
Cyclohexane-d ₁₂	48	40	—	35
Cyclooctane	41	44	—	23
cis-DMCH	26	79	2	6
Adamantane	28	74	3	6
cis-Cyclooctene epoxide ^a	24	77	5	9
syn-Cyclooctane-1,2-diol ^a	98	97	78	86

^a Cyclooctene was employed as a substrate. ^b [Fe(TPA)(CH₃CN)₂]²⁺, Ref. 8a.

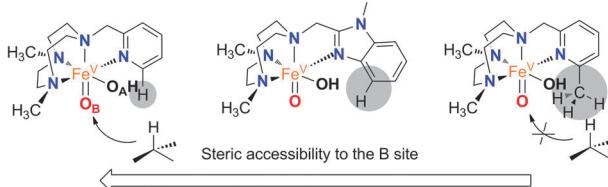


Fig. 2 Comparative analysis of the steric bulk in proximity to site B.

product (up to 79%, *cf.* Table 1). Instead, hydroxylation of secondary C–H bonds occurs with incorporation of ~40% of oxygen atoms from water, suggesting comparable reactivity of both tautomers. In sharp contrast, hydroxylation catalyzed by 3^{OTf} exhibits a relatively small extent (~10%) of water incorporation in hydroxylation of secondary C–H bonds, and negligible (<3%) incorporation in the hydroxylation of tertiary C–H sites, indicating that hydroxylation is almost exclusively performed by O_A .

Therefore, the relative reactivity of the two tautomeric forms of the $[\text{Fe}^{\text{V}}(\text{O})(\text{OH})(\text{L}^{\text{N4}})]^{2+}$ (O) intermediate is finely tuned among the series of catalysts ($1^{\text{OTf}}\text{--}3^{\text{OTf}}$), a fact that contrasts with the small effects exerted when the electronic properties of the pyridine in a series of catalysts is altered.^{8d} Trends observed for $1^{\text{OTf}}\text{--}3^{\text{OTf}}$ may thus be rationalized on the basis of steric effects. The benzyl-imidazole ring introduces steric bulk in the proximity of position B at the iron center that is intermediate between that set by pyridine and 6-Me-pyridine arms (Fig. 2). Accordingly, when secondary C–H bonds are hydroxylated, 1^{OTf} behaves as 2^{OTf} , *i.e.* tautomers O_A and O_B are equally implicated in the C–H oxidation reaction. On the other hand, oxidation of sterically more demanding tertiary C–H bonds yields levels of water incorporation that suggest predominant participation of O_A as in the case of 3^{OTf} , although unlike in the latter case, implication of O_B remains significant (~25%) because steric hindrance at position B induced by the C–C-sp² benzylimidazole moiety is smaller than the one caused by a C–sp³ methyl substituent.

In conclusion, the present work adds to the growing evidence that the coordination environment at non-heme sites opens reactivity scenarios unattainable by hemes. Here we have shown that systematic tuning of the steric properties of the two sites in the *cis*-Fe(O)(X) unit translates into systematic differences in

relative reactivity of the two iron–oxo tautomers. We postulate that analogous steric conditions may influence the relative reactivities of putative tautomers in non-heme iron oxygenases.

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Notes and references

[‡] Analogous product yields and A/K selectivity values were obtained when H₂O (1000 equiv.) was not specifically added.

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