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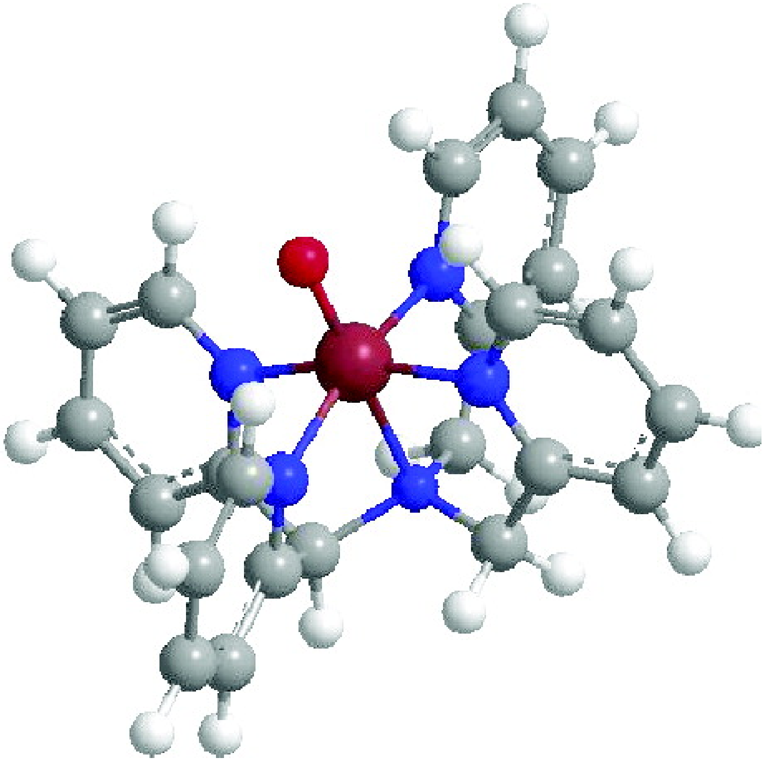

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Theoretical Investigation of C−H Hydroxylation by (N4Py)$Fe^{IV}=O^{2+}$: An Oxidant More Powerful than P450?

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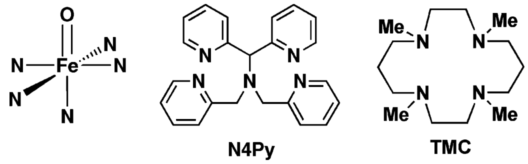
High-valent iron−oxo intermediates are invoked in the catalytic cycles of mononuclear iron enzymes that carry out essential oxidative transformations.[1] Such species have been characterized for heme enzymes such as peroxidases[1a] and for nonheme enzymes[1b] such as TauD.[2] In cytochrome P450, this species was implicated but still awaits full characterization.[3] In heme enzymes, the iron−oxo active species, so-called compound I (Cpd I), is typified by an $Fe^{IV}O$ unit coordinated to a porphyrin in its radical cation state, hence $(Por^{\bullet+})Fe^{IV}O$.[4] Cpd I is a potent oxidant able to oxidize nonactivated bonds; for example, P450 Cpd I hydroxylates inert C−H bonds with bond dissociation energies exceeding 95 kcal/mol. A second intermediate, the corresponding one-electron reduced species, termed Cpd II, involves $(Por)Fe^{IV}O$ [or $(Por)Fe^{IV}OH$][1a] and *is a sluggish reagent for C−H bond activation* compared with Cpd I.[5] However, many nonheme iron enzymes are proposed to utilize $Fe^{IV}O$ intermediates,[1b] analogous to Cpd II, to effect substrate oxidations and even perform C−H hydroxylation (e.g., TauD).

Recently, a family of synthetic complexes has been characterized that form $LFe^{IV}O^{2+}$ intermediates, where L is an N4 or N5 ligand.[6] Notably, the oxoiron(IV) complex of N4Py, shown in Scheme 1, was found to be capable of activating even the strong C−H bond in cyclohexane ($D_{CH} = 99$ kcal/mol). Furthermore, the logarithms of the rate constants of the various reactions exhibited a linear correlation with the C−H bond strengths,[6a,7] thus suggesting that the reactions involved hydrogen abstraction, presumably in a rebound mechanism.[8]

Scheme 1. Ligands in Synthetic $LFe^{IV}=O$ Oxidants



To understand the origins of this oxidative power of the oxoiron(IV) complexes, we use here DFT calculations of cyclohexane hydroxylation by the N4Py complex (N4Py)$Fe^{IV}=O^{2+}$, **K** in Figure 1. Geometry optimization and frequency calculations were carried out at the usual[9] UB3LYP level using the LACVP(Fe)/6-31G(rest) basis set (B1). Single-point calculations, with the larger basis set (B2), LACV3P++**(iron)/6-311++G**(rest), were used for energy evaluation. Solvent effect on the B2 energies was calculated with JAGUAR 5.5.[10] All the data are given in the Supporting Information, while here we focus on the B2 results.

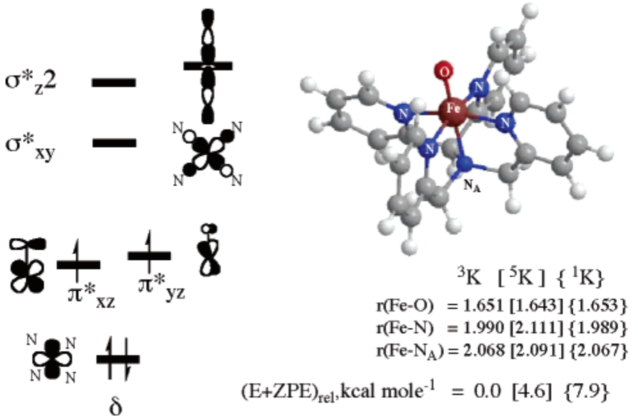


Figure 1. Key orbitals for ^{3}**K**, geometries, and B2 energies for ^{3,5,1}**K**.

Figure 1 shows the d-block orbital energy diagram of ^{3}**K**, alongside the geometries and relative energies in the lowest spin states, ^{3}**K**, ^{5}**K**, and ^{1}**K**. In accord with experiment,[6a] the ground state is the triplet state in a $\delta^2\pi^*_{xz}{}^1\,\pi^*_{yz}{}^1$ configuration. The Fe=O bond length is close to the experimental datum for (TMC)$Fe=O^{2+}$,[6b] and the corresponding stretching frequency is 863 (838 scaled[11]) cm^{-1}, virtually the same as the experimental value (834 cm^{-1}).[6b] ^{3}**K** is followed by a quintet state, ^{5}**K**, $\delta^1\pi^*_{xz}{}^1\pi^*_{yz}{}^1\sigma^*_{xy}{}^1$, and the open-shell singlet state, ^{1}**K**, $\delta^2\pi^*_{xz}{}^1\pi^*_{yz}{}^1$.

The reaction profile for cyclohexane (**C−H**) hydroxylation by ^{1,3,5}**K** is displayed in Figure 2, along with the structures of key species. The reactants, ^{1,3,5}**K** + **C−H**, form clusters (^{1,3,5}**RC**), followed by transition states for hydrogen abstraction, ^{1,3,5}**TS**$_H$. The gas-phase barrier on the triplet surface is 9.6 kcal/mol from the cluster. Inclusion of solvation correction raises the barrier to 11.9 kcal/mol from ^{3}**RC** and to 16.7 kcal/mol from the energy level of the reactants (the free-energy barrier from the reactants can be estimated as 26−27 kcal/mol, by adding the entropic effect due to loss of translational and rotational degrees of freedom).

The gas-phase barrier (9.6 kcal/mol) on the triplet state surface is lower than those calculated for C−H hydroxylation by Cpd I of P450.[12,13] For example, the lowest barrier with ZPE correction for camphor hydroxylation ($D_{CH} \geq 99$ kcal/mol) is 16−17 kcal/mol (relative to the reactant's cluster) in the gas phase and in the protein.[12,13] Similarly, the P450 hydroxylation barrier for the C^2−H bond of propane ($D_{CH} = 99$ kcal/mol) is 14.0 kcal/mol with ZPE correction.[12] Thus, intrinsically, the (N4Py)$Fe^{IV}=O^{2+}$ reagent is more potent than the Cpd I species of P450. A key difference is the stability of the ^{3}**I** intermediate relative to that of the reactants. Here, the C−H activation step for (N4Py)$Fe^{IV}=O^{2+}$ is almost thermoneutral,[14] whereas for the same C−H bond energy, the corresponding P450 reactions are more endothermic.[12] Following the Bell−Evans−Polanyi principle, this excess stability is expected to result in a lower barrier compared with those for P450 Cpd I. A minor contribution to the stability of ^{3}**I** is the stronger FeO−H bond,

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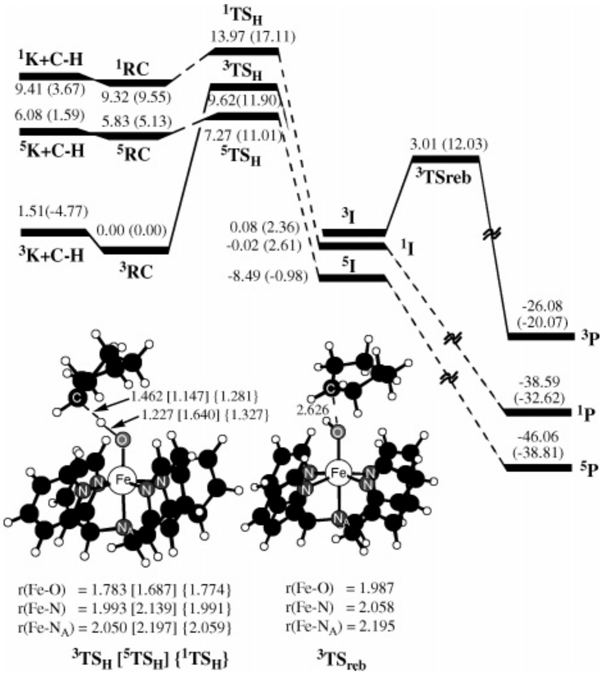

Figure 2. Energy profiles (in kcal/mol) for hydroxylation of cyclohexane (**C−H**) by ^{1,5,3}**K**. The values out of parentheses correspond to B2 data with ZPE correction; the values in parentheses include also solvation correction (using a dielectric constant, $\epsilon = 37.5$, for acetonitrile).

after H-abstraction by (N4Py)Fe^{IV}═O^{2+} compared with (Por$^{\bullet+}$)-Fe^{IV}═O (84.0 vs 81.5 kcal/mol, respectively, with B1 with ZPE correction).[12] The major contribution that stabilizes ^{3}**I** is the strong interaction (7.1 kcal/mol in B1 with ZPE) of the cyclohexyl radical with the dipositive (N4Py)Fe^{III}OH^{2+} moiety. This stabilization carries over to ^{3}**TS**$_H$, where the positively charged moiety of the reagent stabilizes the three-centered/three-electron moiety O⋯H⋯C of **TS**$_H$. Thus, the high positive charge of (N4Py)Fe^{IV}═O^{2+} is the root cause why this reagent is intrinsically a better C−H activator than a Cpd I species, even though (N4Py)Fe^{IV}═O^{2+} is more sterically encumbered compared with Cpd I. Because of this dipositive charge and its delocalization in **TS**$_H$, the loss of solvation in the **TS**$_H$ species will make a significant contribution to the reaction barrier in solution. As such, *this reagent should exhibit a strong solvent effect on C−H hydroxylation*.

Following H-abstraction, the intermediate ^{3}**I** undergoes rebound to form the alcohol complex, ^{3}**P**. The rebound barrier is seen to be large (9.8 kcal/mol at the B2 + ZPE + solvation level), significantly larger than in P450 hydroxylation of primary and secondary C−H bonds.[15] The rebound step of ^{3}**I** should have been slow and rate determining were it not for a crossing of the triplet state by the energy profiles of the singlet and quintet states, near the intermediate, ^{3}**I**, and the ^{3}**TS**$_H$ species. The quintet state species are especially stable due to multiple exchange interactions among the electrons in the open-shell d-block configuration. For example, the intermediate, ^{5}**I**, has a half-filled d-orbital shell ($\delta^1\pi^{*2}\sigma_{z^2}{}^{*1}\sigma_{xy}{}^{*1}$; see Figure S10), *which leads to significant exchange stabilization*. With such an electronic configuration for ^{5}**I**, once the cyclohexyl radical assumes a rebound position, the respective process has no barrier since it involves an electron relay from the organic radical in ^{5}**I** to the low-lying δ-orbital (similarly, for the singlet rebound, the electron is relayed to the π^*-orbital).[15] Since the spin−orbit coupling interaction between the triplet and the quintet states is expected to be significant,[16a] the spin-state crossing may provide a lower energy pathway that promotes the reaction and minimizes the lifetime of the organic radical in ^{3}**I**. This is different from the situation in P450[12,13,15] and is reminiscent of the gas-phase reactions of iron−oxo cations.[16b] Since the spin inversion probability has an inverse temperature (*T*) dependence, the spin-state crossing option can be tested by following, at variable *T*,[16] the rearrangement patterns of chiral substrates or those that produce radicals that can rearrange.

In sum, the C−H hydroxylation of cyclohexane by the nonheme oxidant, (N4Py)Fe^{IV}═O^{2+}, is calculated to be more reactive than P450 Cpd I and is predicted to involve multistate reactivity with a strong solvent effect, and a *T*-dependent stereoselectivity reflecting spin crossover effects.[16]

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Supporting Information Available: Six tables and 18 figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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