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Fundamental Role of Exchange-Enhanced Reactivity in C-H Activation by S=2 Oxoiron(IV) Complexes

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Abstract



It is shown that H-abstraction reactivity by oxoiron(IV) complexes with a quintet ground state is highly enhanced due to exchange-stabilization *endowed by the increased number of the exchange*

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d-d interactions near the transition state. It is postulated that nonheme enzymes evolved to make use of this fundamental mechanism in activation of strong C-H bonds.

Keywords

nonheme iron enzymes; iron-oxo; TSR; exchange stabilization; DFT calculations

Nonheme iron chemistry has led to the identification of a variety of iron(IV)-oxo intermediates, which perform oxidative processes such as H-abstraction and oxo-transfer reactions to a variety of molecules.[1,2] The advent of both enzymatic and synthetic examples has revealed a fundamental dichotomy. Thus, whereas the known enzymatic species, e.g., in taurine/ α -ketoglutarate dioxygenase (TauD),[3] utilize iron(IV)-oxo intermediates with a quintet spin (*S*=2) ground state, the great majority of the synthetic iron-oxo species have triplet ground states (*S*=1) and low-lying quintet states.[2a,c] DFT calculations suggest that the synthetic reagents should react via two-state reactivity (TSR), [4] whereby the excited *S*=2 state which has a small barrier cuts through the larger triplet state barrier and mediates the H-abstraction process.[4,5] Given this enhanced *S*=2 reactivity, there is an intense search for ways to design new iron-oxo reagents which have a quintet ground state and which may therefore be potent C-H bond activators, like the natural enzymes.

One of us,[6] has recently prepared two such S=2 reagents and compared their H-abstraction activities to those of the synthetic complexes that possess the more common S=1 ground state. These results generated however, a bag full of surprises, which are addressed herein by means of DFT calculations. Shown in Figure 1 are DFT calculated iron(IV)-oxo complexes along with their key geometric features, and spin state information. The isolated complex with an S=2 ground state is TMG₃trenFe(IV)O²⁺ (1),[6a] which possesses a trigonal bipyramidal iron coordination, typified by two-below-two-below-one d-orbital block,[3b] and hence a quintet ground state, well below the S=1 state. Surprisingly, however, 1 exhibited a rather sluggish H-abstraction reactivity even towards the weak C-H bonds of 1,4-cyclohexadiene (CHD). Thus, 1 was slightly less reactive than N4PyFe(IV) O^{2+} 2 and five times more reactive than $TMC(AN)Fe(IV)O^{2+}$, 3;[6b] both of which are thought to react via TSR.[4] To add to the puzzle, the putative Tp(OBz)Fe(IV)O, 4, which was proposed to form upon oxygenation of Tp(benzoylformate)Fe(II) as a model for TauD, was found to be highly reactive and capable of activating even the strong C-H bond of cyclopentane (BDE = 96.3 kcal mol⁻¹).[6b] Note that in the S=2 state, ⁵4, Fe loses one of the benzoate arms and becomes a pentacoordinated square pyramid with a basal Fe(IV)-oxo moiety (Fig. 1). Thus, it is this weaker ligand field that stabilizes S=2 relative to the hexacoordinated S=1. Indeed, as can be seen from Figure 1, 4 is computed to involve degenerate S=1 and S=2 states.[7] So, in 4 a competition is expected between the two spin states to effect C-H activation; which state dominates? In summation, the experimental relative reactivities of the four Fe=O reagents order in a puzzling sequence: $4 \gg 2 \ge 1 > 3$. What is the origin of this reactivity pattern, and what are the electronic and steric factors that shape this trend? Answering this question is important for establishing rules of design of effective catalysts for C-H activation.

To answer these questions we studied the reactivities of 1-4 towards H-abstraction from CHD. The geometries of all the critical species along the H-abstraction paths of 1-3, which are di-positively charged, were optimized at the B3LYP/B1(CH₃CN) (B1 is LACVP) level at the reaction solvent, to minimize self-interaction errors which cause artificial electron transfer in some of these systems.[8] For **4**, which is neutral and hence less subject to these particular errors,[8] we used B3LYP/B1. All energies were subsequently estimated using a

Scheme 1 shows the types of energy profiles unraveled by the calculations, where the reactant clusters (^{3,5}RC) and ^{3,5}I are genuine minima and ^{3,5}TS_H genuine transition states. Table 1 collects the barrier and reaction energy data. All calculated barriers are relative to the lowest RC (scheme 1), and hence the free energies do not include the effect of loss of entropy due to association (estimated experimentally to be -18 eu for strong complexation[9]), which will increase all free energy barriers by a value of 4.4 kcal/mol at T = 243K.[9] For calibration, we show the experimental ΔG^{\ddagger} datum for H-abstraction from taurine by the iron(IV)-oxo species of TauD, with the *S*=2 ground state.[3c] Since the C-H bond of taurine has a larger bond dissociation energy (BDE) than those of CHD (by ~23 kcal mol⁻¹, Table S8), one might expect a much lower barrier for CHD. Indeed, DFT calculations[5a] for abstraction of the allylic C-H bond in propene by iron(IV)-oxo species of TauD gave a barrier of only 5.4 kcal mol⁻¹.

Inspection of the table reveals a few trends: Firstly, the triplet state barriers are larger than the barriers for the quintet state. In all cases, the quintet is also the ground state of the H-abstraction intermediate (⁵I, Scheme 1). Secondly, because of the large spin-state energy gap, it is clear that 1 will react exclusively via the S=2 ground state. The ΔG^{\ddagger} datum for 1 seems close to the experimental value,[6a] but it does not include the entropic effect due to association.[9] Regarding 4, it is seen that, despite the degeneracy of the triplet and quintet states of the iron-oxo reagent itself, its observed high reactivity[6b] must be ascribed to its reaction through the S=2 state, which has a much smaller barrier than the competing S=1 state. The much higher reactivity observed experimentally for 4 compared to 1,[6] is also nicely reproduced by the calculations.

Comparison of **2** and **3** reveals that the barriers on both S=1 and S=2 states are lower for **2**, which is in accord with experimental observation. Furthermore, the S=2 barriers are gauged relative to the S=1 reactant cluster species. But in fact, the S=2 surface for **2** is barrier free, whereas for **3** there is a barrier of 4-7 kcal mol⁻¹ on the different energy scales. **2** and **3** were postulated before to react via TSR, with crossover from the S=1 to the S=2 state.[4c] Thus, if we assume that **2** and **3** react via the S=2 state with a spin crossover probability close to unity, both reagents would then be predicted to be highly reactive, and by a few orders of magnitude larger than **1**. This is of course in discord with the experimental data. [6a] As such, we may conclude that **2** and **3** activate CHD by a TSR scenario where the reactions start on the S=1 surface and then cross over to S=2, but with a weak probability[4c, 10] that lowers the rate constant to the value observed experimentally.[6a] Adding to the S=2 free energy barriers the contribution of 4.4 kcal mol⁻¹ due to the loss of entropy[9] in the formation of ³RC, such probabilities can be roughly estimated as $\leq 10^{-3}$, in accord with previous estimates.[4c]

The computed high barrier and the experimentally-observed[6a] sluggish reactivity of the S=2 state of 1 vs. the very low barriers on the S=2 surfaces of all other reagents may seem odd. In the first place, we might ask: *Is there a fundamental reason why the* S=2 *state should have such small barriers*? Figure 2 shows schematic orbital occupancy changes,[4b] upon going from the reactant clusters ($^{3,5}RC$) to the intermediate after H-abstraction ($^{3,5}I$). It is seen that the triplet process involves a shift of a β electron to a π^* d-orbital of the iron-oxo reagent, while forming a CHD radical in the φ_C orbital. By contrast, during the quintet reaction an α electron shifts to the $\sigma^*_{z^2}$ d-orbital.[4a,b] As such, in the triplet reaction the number of the stabilizing d-d exchange interactions on the metal center is diminished in $^{3}TS_H$. By contrast, in $^{5}TS_H$ the d-d exchange is augmented relative to ^{5}RC by *four new*

interactions. Thus, ⁵TS_H is strongly stabilized compared to ⁵RC by exchange interactions that lower the electron-electron repulsions. This differential stabilization in turn *flattens the* S=2 energy profile. Furthermore, since ³TS_H is not stabilized by exchange, ⁵TS_H becomes the lowest species, [4d] at the transition state region, even in 2 and 3 where the S=2 starts as an excited state. The spin-states thus interchange in energy in the TS region, due to the different behavior of the corresponding exchange interactions. Hence, in general, the barrier on the S=1 state is high, while that on S=2 surface is low due to "exchange enhanced reactivity".[4a,b;5]

The orbital occupancy evolution diagram (Fig. 2) defines also *structural selection rules* for the TSs: the TS will assume the structure that optimizes the orbital overlap between the σ_{CH} and the corresponding accepting orbital, π^* or $\sigma^*_z^2$. The structural information for ${}^{5/3}TS_H$ in Figure 3 indeed illustrates these selection rules, as well as the trends in the barrier data in Table 1. Thus, the elongated Fe-N_A bonds and the Fe–O–H angles of ~180° in ${}^{5}TS_H$ reflect the occupancy of the $\sigma^*_z^2$ orbital[4,11] during the *S*=2 process, while the short Fe-N_A bonds and the small Fe–O–H angles of ~121–124° in ${}^{3}TS_H$ are in accord with the proposed occupancy of the π^* orbital, during the *S*=1 process. Additionally, the O---C---H moieties of 1–4 show that ${}^{5}TS_H$ is earlier than the corresponding ${}^{3}TS_H$, in terms of C–H bond breaking and O–H bond making, in accord with the relative barriers on the two spin surfaces. As such, the "*exchange-enhanced reactivity*" of the *S*=2 state vs. the low reactivity of *S*=1 is a fundamental trend that will be true irrespective of computational accuracy.

The remaining question then is: why is 1, which to begin with has a quintet ground state, such a sluggish C-H activator? It was postulated[6a] that this was due to steric effects imparted by the tetramethylguanidino substituents of the TMG₃tren ligand. To test this hypothesis we deleted these substituents in 1_t, and indeed, as seen in Table 1, the *S*=2 barrier for the H-abstraction reaction by 1_t is lowered dramatically to 3.5 kcal mol⁻¹. Thus, the aforementioned "*exchange-enhanced reactivity*" manifests nicely in ⁵1_t. In fact, the sluggish reactivity of 3 compared with 2 is also due to poorer access to the Fe=O moiety in 3 (Fig. S8).[11a] Clearly, having a quintet ground state, by itself, is not sufficient to impart high reactivity on the iron(IV)-oxo reagent if steric fences prohibit substrate access.

The reagent **4** seems to be an ideal solution for creating mimetic reagents of the enzymatic iron-oxo species. Its benzoate ligand (see Fig. 1) provides an in-situ mechanism for generating a low-lying S=2 state by release of one of its arms from the Fe coordination sphere similarly to the formation of the iron-oxo species of TauD.[3] The Fe(IV)O moiety of **4** is further protected by the 3,5-phenyl substituents on two pyrazole ligands, but in a manner that creates a cleft[6b] that admits substrates selectively without imposing a great deal of steric hindrance. These properties make **4** a very potent C-H activator with shape selectivity. [6b]

In conclusion, the heightened reactivity of the S=2 state of iron(IV)-oxo reagents towards C-H bond activation originates in *exchange-enhanced reactivity* wherein the increased number of the exchange d-d interactions (Fig. 2) *upon going from the reactant cluster en route to the transition state* flattens the S=2 energy profile and lowers its barrier. The S=2 barriers measured from the corresponding reactant cluster, ⁵RC (Scheme 1) are extremely small, e.g., 3.5 and 6.3 kcal mol⁻¹ for 1_t and 4, respectively, and even zero in 2. Only steric effects can raise these barriers as found in 1. The nonheme enzymes like TauD apparently evolved to have iron(IV)-oxo reagents with a S=2 ground state in order to optimize the C-H bond activation of strong C-H bonds like in taurine, *by virtue of exchange enhancement*.

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Figure 1.

Key optimized bond distances in Å (B3LYP/B1(solvent)). Values in square brackets are S=2/S=1 relative energies (B2) in kcal mol⁻¹ for **1–4** (B1 and B2 are specified in the text).

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Figure 2.

Orbital occupancy change during H-abstraction on the S=1 and S=2 states of an LFe(IV)O^{z+} reagent (the drawn orbitals are specific to 2). The ^{3/5}I occupancies are related to the respective ^{3/5}TS_H.



Figure 3.

Key structural features (distances in Å, angles in degrees) in the N_A-Fe-O---H---C moiety of ${}^{5}TS_{H}/{}^{3}TS_{H}$ of **1–4**.

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Scheme 1.

Schematic representations of the energy profiles for the H-abstraction reactions of $1\!-\!4$ with CHD. RC is the reactant cluster.

Table 1

Computed Barriers and Reaction Energies (kcal mol^{-1}) for H-Abstraction Reactions from CHD (C₆H₈) by LFe(IV)O^{z+} Reagents

L[a]	$\Delta E^{\ddagger}/\Delta E^{\ddagger}+\mathrm{ZPE}/\Delta G^{\ddagger}^{[a]}$		$\Delta G^{\ddagger}_{ex}[e]$	$\Delta G_{\rm rx}[f]$
	<i>S</i> =1	S=2		S=1/S=2
TMG ₃ tren,1	30.9/26.7/31.3	14.9/11.5/15.6	14.0	-3.1/-12.3
$\mathbf{1_t}^{[b]}$		3.5[c]/_/_	-	
N4Py, 2	12.9/10.0/13.0	10.8/5.4/6.5	14.0	-15.5/-17.9
TMC(AN), 3	20.3/16.6/18.8	12.0/6.2/7.1	16.1	-8.1/-15.9
Tp(OBz), 4	15.1/12.3/16.5	7.7/5.4/6.3	-	-16.1/-28.7
TauD		_/5.4[d]/_	14.8	

[a]**1–3** were optimized with solvent included. Barrier data (B3LYP/B2 with solvent corrections), relative to the ground state of the reactant cluster (Scheme 1).

[b] Truncated **1**.

 $[c]_{\Delta E^{\ddagger}}$ datum.

[d] ZPE corrected barrier for an allylic C-H bond.[5a]

^[e]Calculated with the Eyring equation using rate constants; for **1–3** from ref. 6a and for TauD from ref. 3c.

[f] The energies of the S=1/S=2 intermediates, relative to the lowest reactant cluster.