Theoretical Investigations into C–H Bond Activation Reaction by Nonheme MnIVO Complexes: Multistate Reactivity with No Oxygen Rebound

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Supporting Information

ABSTRACT: Recently published experimental results on a nonheme synthetic [(Bn-TPEN)MnIVO]2+ complex reveal that it is capable of activating strong C–H bonds. However, the final products are shown to contain MnIII instead of the expected MnII, which should be formed if a rebound mechanism similar to what is assumed for heme FeIVO was to occur. It was proposed that the substrate radical generated during H-abstraction dissociates from the MnIIIOH complex and undergoes an additional reaction to a second molecule of MnIVO, leading to MnIII. Density functional calculations reveal the root cause of why a follow-up rebound to form MnII and alcohol is not preferred in this system. It is further shown that nonheme MnIVO has a more complex spin-state manifold during C–H activation reactions compared with FeIVO, and that spin-state matters in oxidative chemistry of metal-oxo reagents.

SECTION: Molecular Structure, Quantum Chemistry, and General Theory

Synthetic nonheme FeIVO and FeVO compounds attract high interest in bioinorganic chemistry,1−9 however, their counterpart MnIVO has been much less studied. Although not as ubiquitous as FeIVO, MnIVO still performs important reactions for instance in oxygen-evolving complex in Photosystem II.10−13 Nonheme MnIVO systems are therefore of prime interest, not the least for their possible use in a future synthetic Photosystem II equivalent, especially because efforts have been successful in synthesizing such a compound where the oxygen is derived from water.14 However, it is only very recently that a nonheme synthetic MnIVO system was shown to be powerful enough to activate the C–H bond of cyclohexane.15 Interestingly, product analysis upon reaction with cyclohexane as a substrate revealed a MnIII product species rather than MnII, which would be expected if the reaction mechanism was analogous to the rebound mechanism of heme FeIVO.16 An alternative reaction mechanism that differs from the standard rebound model in heme FeIVO was therefore suggested. In this mechanism, instead of rebinding, the substrate radical dissociates to react with a second MnIVO molecule (Scheme 1), thereby comprising a 2:1 catalyst:substrate stoichiometric reaction. This would imply that the energy barrier for rebound is higher than the energy required for the substrate radical to dissociate from the MnIIIIOH intermediate and find another MnIVO molecule. Indeed, we have found such a preference in a recent study of nonheme FeIVO as well.17 Therefore, theoretical calculations seem to be called for to explain this unexpected occurrence of MnIII species.

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but differently charged ligands yielded different oxidation states of the metal (i.e., (L)MnIVO vs (L*)MnVIO). In enzymatic settings, the difficulty of these studies is exemplified by calculations on the reaction mechanism of manganese-dependent homoprotocatechuate 2,3-dioxygenase (MndD). Initially, a sextet rate-limiting step was found that involved the formation of a MnIIIIOH species. Subsequent studies, however, revealed that the rate-limiting step should be in fact the spin crossover from sextet to quartet at a minimum energy crossing point just prior to the transition state forming MnIIIIOH, lowering the barrier by 7.4 kcal/mol. In synthetic settings, initial calculations on the MnIV corrolazine complex seemed to show that a closed shell S = 0 state was responsible for C−H activation reactivity of 9,10-dihydroanthracene because a lower barrier than the triplet counterpart was found. However, the study also overlooked possibilities of additional triplet spin states, thereby missing a lower transition state due to exchange-enhanced reactivity (EER). All of these examples underscore the need for a full and meticulous theoretical treatment of manganese-oxo species to understand the finer features of this species.

In this study, we have explored the feasibility of rebound versus dissociation reactions for two nonehmic synthetic MnIVO compounds, [(Bn-TPEN)MnIVO]2+ (1) and [(N4Py)MnVIII]2+ (2) (Bn-TPEN = N-benzyl-N,N,N′,N′-tris(2-pyridylmethyl)ethane-1,2-diamine, N4Py = N,N-bis(2-pyridylmethyl)-N-bis(2-pyridyl)methylamine; see Scheme 2). The substrate used in the calculations is cyclohexane, from which an equatorial hydrogen atom is abstracted. We consider four different spin-state configurations in this reaction, totaling 74 different optimized structures, and novel insights emerge into the reaction preferences.

**Reactant Complex (RC) States for 1.** Previous studies on FeIVO species show that there are, in principle, only two spin states (S = 1 and S = 2) that participate in a C−H activation reaction. Below we show that the corresponding MnIVO complexes have richer electronic configuration possibilities. In agreement with experiments, the ground state of 1 was found to be the intermediate-spin state (S = 3/2, where the left superscript designates the multiplicity M = 2S + 1, a and b indicating the presence of two different S = 3/2 states). Interestingly, we found another intermediate-spin configuration (S = 3/2, 4b), which is in fact connected to the lowest C−H activation transition state (4bTS1, 13.0 kcal/mol, Figure 1) and the lowest intermediate structure (4bInt, 3.0 kcal/mol, vide infra). The difference between the intermediate-spin states 4a and 4b is shown in Figure 2. 4a has an α-electron in the π*xy orbital, whereas 4b has it in the π*yz orbital instead. The reason why 4a does not also accept an α-electron is that the empty π*yz orbital has no contribution on the oxygen atom; hence, this orbital cannot interact with the substrate’s C−H orbital. Instead, 4a abstracts a β-electron from the substrate to the π*yz orbital. The reason why 4b does not also accept an α-electron is that the empty π*yz orbital has no contribution on the oxygen atom; hence, this orbital cannot interact with the substrate’s C−H orbital. Instead, 4b abstracts a β-electron from the substrate to the π*yz orbital, which is delocalized on the oxygen and can interact with it. This, however, reduces the exchange interactions between the unpaired electrons, and 4bTS1 is high in energy (27.4 kcal/mol, Figure 1). In the intermediate state (4bInt), the electronic configuration is in an excited state, with the π*xy orbital doubly occupied and the lower lying δ orbital singly occupied (Figure 2, first column). Hence, it needs to go through an extra step of relaying down the β-electron to the lower orbital and getting stabilized by 5.4 kcal/mol (Figure 1). Rather than going through all of these high-energy states, the lower energy 4bTS1 species will mediate this part of the reaction resulting in the 4bInt state, not the least because the spin−orbit coupling (SOC) generated due to shifting an electron from the π*xy orbital to π*yz in the reactant state may be too high in energy at every step of the reaction mechanism and hence not relevant (data are found in the SI).

**C−H Activation Reaction.** Whereas 4aRC is the ground state in the reactant stage, 4aRC maximizes the EER at the transition state (4aTS1) and intermediate (4aInt) states by accepting an α-electron from the substrate to the π*xy orbital. The reason why 4a does not also accept an α-electron is that the empty π*yz orbital has no contribution on the oxygen atom; hence, this orbital cannot interact with the substrate’s C−H orbital. Instead, 4a abstracts a β-electron from the substrate to the π*yz orbital, which is delocalized on the oxygen and can interact with it. This, however, reduces the exchange interactions between the unpaired electrons, and 4bTS1 is high in energy (27.4 kcal/mol, Figure 1). In the intermediate state (4bInt), the electronic configuration is in an excited state, with the π*xy orbital doubly occupied and the lower lying δ orbital singly occupied (Figure 2, first column). Hence, it needs to go through an extra step of relaying down the β-electron to the lower orbital and getting stabilized by 5.4 kcal/mol (Figure 1). Rather than going through all of these high-energy states, the lower energy 4bTS1 species will mediate this part of the reaction resulting in the 4bInt state, not the least because the spin−orbit coupling (SOC) generated due to shifting an electron from the π*xy orbital to π*yz in the reactant state may be too high in energy at every step of the reaction mechanism and hence not relevant (data are found in the SI). As for the high-spin sextet state, in the conventional assignment, MnIVO has a d3 configuration, and hence the sextet state is in fact usually not even considered. However, MnIVO possesses two more valence orbitals from the oxygen atom, and because the oxygen and Mn orbitals vary their mixing along the reaction coordinate, it is justified to talk about a seven valence electron configuration for MnIVO that includes also the lower lying bonding orbitals πxy and δxy (Figure 2). This is done here because we found that the sextet state is potentially relevant later on in the reaction mechanism (vide infra). However, because the high-spin state has a high C−H activation transition state energy (4bTS1, 22.7 kcal/mol, Figure 1), we conclude that the high-spin state is also not viable in this part of the reaction.

![Figure 1](https://doi.org/10.1021/jz301241z.J. Phys. Chem. Lett. 2012, 3, 2851−2856)
be high. Because the $M = 4a$ state is consistently high in energy for the remainder of the reaction (see the SI), it is not discussed any further.

In the intermediate stage, the high-spin $^5\text{Int}$ state is potentially relevant because its energy is virtually degenerate to $^5\text{Int}$. This is because the two states differ only by the spin direction on the substrate (Figure 2). Hence, one could, in principle, imagine that going from $^5\text{Int}$ to $^5\text{Int}$ would be a swift process because it requires only a spin flip at the substrate radical, but because hardly any SOC is involved in this case, the spin flip rate should be similar to the one of free organic radicals in solution. As shown in Figure 3 as a loopback, a finite reaction-rate for the spin inversion is equivalent to an effective “barrier” and a corresponding spin inversion junction ($4b \rightarrow ^6\text{TS}_{\text{int}}$). The relevance of this is discussed below.

**Choice of Reaction Pathways.** In the intermediate stage, the reaction can branch out in different possible directions. We have investigated three reactions: alcohol formation through rebound hydroxylation reaction, alkene formation through desaturation reaction, and simply a dissociation reaction forming a substrate free radical that can react with a second Mn$^{III}$O species (for instance according to Scheme 1). As it turns out, the desaturation reaction has a higher barrier than the rebound reaction in all possible spin-state cases. Therefore, the discussion will center on the rebound and dissociation processes, and the desaturation data is relegated to the SI.

Following the assumption that a rebound reaction could occur, we find that the two lowest transition states $^4\text{TS}2$ and $^6\text{TS}2$ are at 15.8 and 3.9 kcal/mol, respectively, relative to $^4\text{RC}$ (see Figure 3). The reason why the latter barrier is so low is that $^4\text{TS}2$ has five unpaired electrons at the transition state (Figure 2), which again enjoys EER and considerably lowers the barrier compared with the other configurations. Considering only this energy aspect, it would lead to the conclusion that the rebound step should be preferred over dissociation because $^4\text{TS}2$ lies lower in energy than the dissociated state ($^4\text{P}_{\text{dis}} - 4.6$ kcal/mol). However, one needs to remember that the reaction then proceeds through a spin inversion junction $4b \rightarrow ^6\text{TS}_{\text{int}}$. For this to be competitive with dissociation, the spin flip rate should be equivalent to a barrier of at most 1.6 kcal/mol, which is the dissociation energy of the Mn$^{II}$OH/radical complex ($^4\text{P}_{\text{dis}} - ^4\text{Int}$). Using the Eyring equation, such a barrier would require a spin-flip rate of $10^{11}$ s$^{-1}$ (or faster) at room temperature. This is unlikely because the corresponding SOC is small, and we assume here for the sake of argument that the rate of spin-flip is on the scale of $10^9$ s$^{-1}$, which is probably still much overestimated based on analogous processes. The reaction rate would translate into a barrier of 5 kcal/mol, and consequently the overall lowest energy transition state for the rebound reaction lies at 8.0 kcal/mol ($E(^6\text{Int}) + 5$ kcal/mol), 4.1 kcal/mol higher than the rebound $^4\text{TS}2$ (3.9 kcal/mol). The choice of the reaction pathway is therefore between $4b \rightarrow ^6\text{TS}_{\text{int}}$ and $^4\text{P}_{\text{dis}}$. Hence, the dissociation in the intermediate stage would compete favorably with the spin flip in the radical complex. This leads to the conclusion that the high-spin state is in fact not relevant at all to any stage of the reaction.
mechanism, as $^6$TS1 is high in energy and $^6$TS2 is not even accessible at a relevant time-scale vis-à-vis dissociation. The next lowest rebound barrier ($^{4b}$TS2) is also clearly too high to be competitive with dissociation. In addition, even if the spin flip is faster than expected and $^{6b} \rightarrow ^{6c}$TSint is lower than 8.0 kcal/mol, the reaction will only lead to the $^6$Int state. From here it must go through a second choice of rebounding or dissociating ($^6$TS2 vs $^6P_{ud}$), which are only 0.7 kcal/mol apart in electronic energy. Whereas $^6$TS2 is nominally lower than $^6P_{ud}$ in this electronic energy scale, the entropy effects will largely favor dissociation; therefore, dissociation may be preferred on a free-energy scale.

Reaction Mechanism Using 2. The reaction mechanism discussed above does not deviate significantly when using oxidant 2. It is known that 2 is less reactive than 1, as reflected in the lowest rate-limiting barrier ($^{4b}$TS1) being 6.5 kcal/mol higher than that of 1 (see the SI). Apart from the different specific numbers, the conclusions drawn from 1 are all applicable to 2. The only part that is somewhat conceptually different is the low-spin $^4$TS2 state, where instead of transferring an electron to $\pi^*_{yz}$ as with 1 the electron is transferred to $\pi^*_u$ instead in 2. Considering the high energies of the low-spin state, however, this is hardly relevant.

Theoretical Comparison of FeIVO versus MnIV/O. The comparison between FeIVO and MnIV/O reactions reveals some interesting features, not hitherto considered. Calculations and experiments confirm that nonheme FeIVO reactions in fact should yield more dissociated rather than rebound products, at least if using cyclohexane as substrate (unpublished results). For MnIV/O, the attention to the dissociated products has been awakened recently due to the finding of a MnIII product (Scheme 1). The reason for the occurrence of the dissociated products is, however, slightly different for the two metal-oxo species. In FeIVO, the high-spin state is dominant at both the TS1 and Int stage due to its lower energy. This species then has a direct choice of rebounding or dissociating, with the latter one being preferred. In the MnIV/O case, the preferred spin-state in the intermediate stage is $^{4b}$Int, which is nascent directly from the H-abstraction $^{4b}$TS1, and $^6$Int lies close in energy. Here it has the choice of either spin flipping from $^{4b}$Int to $^6$Int or dissociating to yield a free alkyl radical. If against expectations MnIII(OH) chooses the spin flip, then it will face another choice for the second time: rebound or dissociation. Hence, the rebound process for MnIV/O faces a double challenge and may be more difficult to perform than with FeIVO.

Accepting that TS2 is of no relevance in the MnIV/O reaction (as the reaction goes to dissociation instead), a comparison of TS1 barrier heights should correlate with the reactivity rate of the species. Interestingly, calculations on the [(Bn-TPEN)-FeIV(O)]$^{2+}$ species show that 1 has a lower rate-limiting TS1 by 1.2 kcal/mol (unpublished results), hence showing a potential of being more reactive. Available experimental data of cyclohexane C–H activation at room temperature provide some support for the prediction, showing for 1 a faster rate constant ($3.3 \times 10^{-3} \text{ M}^{-1} \cdot \text{s}^{-1}$) than for [(Bn-TPEN)-FeIII(O)]$^{2+}$ ($3.9 \times 10^{-4} \text{ M}^{-1} \cdot \text{s}^{-1}$). However, as the reactions were conducted with different experimental conditions, the comparison should be considered with caution. Hence, further experiments are under way.

In conclusion, the electronic structures of nonheme MnIV/O species during C–H activation reactions have been mapped out in detail and found to be more complicated than that of FeIV/O.

We have investigated four possible electronic configurations and found interplay of at least two quartet states. The sextet state has a low rebound barrier and is a potential mediating spin state but is excluded due to higher barriers in spin crossing into this state compared with a simple dissociation. The experimental suggestions of nonheme MnIV/O species dissociating at the intermediate state to perform a secondary reaction are therefore reasonable. The calculations also predict that the MnIV/O species can compete in oxidation power with that of FeIVO.

### COMPUTATIONAL METHODS

Density functional theory (DFT) calculations were done using Gaussian 09 package at B3LYP/LACV3P*/+//LACVP level, with solvent (acetonitrile) effects included as a dielectric medium through the CPCP scheme, even in the geometry optimization steps to avoid self-interaction errors. By default, the energy values presented are calculated at this level. As others have pointed out, this approach invalidates adding dispersion or thermal effects taken from frequency calculations to obtain the free energies because the parameterized solvation energy already includes part of the free energy. We have, however, for the sake of formality, calculated these values and are including them in the SI but excluding them from the discussion above. Alternative functionals (B3LYP* and BP86) were used in single-point evaluations of 1 and found to not to change the spin state ordering (see SI, Table S1).

### ASSOCIATED CONTENT

#### Supporting Information

Detailed energies, geometries, and Mulliken spin density distribution of all of the species considered here and full refs 10, 14, and 36. This material is available free of charge via the Internet at [http://pubs.acs.org](http://pubs.acs.org).

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**Notes**

The authors declare no competing financial interest.

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### REFERENCES


