Understanding the reactivity of Mn-oxo porphyrins for substrate hydroxylation: theoretical predictions and experimental evidence reconciled

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Abstract

The Mn-oxo porphyrin (MnOP) mechanism for substrate hydroxylation is computationally studied with the aim to better understand reactivity in these systems. Theoretical studies suggest Mn(V)OP species as very reactive intermediates with thermally accessible reaction barriers represented by low spin/high spin crossover occurring in the Mn(V)OP oxidant, and kinetics for selected Mn(V)OP species indeed find high reactivity. On the other hand, MnOP complexes lead to low yields in catalytic hydroxylation reactions of several different substrates, suggesting low rate constants and high reaction barriers. The origin of this inconsistency is very important to understand the reactivity of Mn-oxo porphyrins and to improve the catalytic conditions. In this work we use the toluene hydroxylation by Mn(V)OP(H₂O)⁺ complex as a case study to gain deep insight into the reaction mechanism and to check that it should indeed have high reactivity. Minimum energy crossing point (MECP) results on H-abstraction process from toluene indicate a first crossover from a singlet to a triplet spin state of the Mn(V)OP(H₂O)⁺ species, which represents the rate-determining step with a thermally accessible barrier, followed by a very facile H-abstraction by the triplet complex. Issues concerning i) the validation of the level of the DFT theory employed (BP86) to describe the singlet-triplet energy gap in the Mn(V)OP(H₂O)⁺ system vs. highly accurate DMRG-CASPT2/CC calculations and ii) the influence of the axial ligand (X = none, Cl⁻, CH₃CN, OH⁻ and O²⁻) on MnOP reactivity, which models the different experimental conditions, are addressed. The ligand trans

influence mainly controls the reactivity through the singlet-triplet energy gap modulation, with the porphyrin ruffling distortion also finely tuning it. Finally, a stepwise model for the H-abstraction process is proposed which allows a direct comparison between the calculated and experimentally measured Gibbs free activation energy barriers (R. Zhang, J.H. Horner, M. Newcomb J. Am. Chem. Soc. 2005, 127, 6573-6582). The low yields in catalysis are shown not to be due to low reactivity of Mn(V).

Introduction

Despite the large body of literature on the reactivity of Mn-oxo porphyrins (MnOP) complexes,^{1-12, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12} there is still a conundrum to be solved. It clearly emerges when one compares various theoretical and experimental results concerning the reactivity of Mn-oxo porphyrins for substrate hydroxylation. Synthetic biomimetic systems based on Mn-porphyrins^{13,14} have been shown to be catalysts for the hydroxylation and epoxidation of a wide range of organic substrates. A very important goal to improve the catalytic conditions of such MnOP-mediated hydroxylation reactions is to gain a higher level of understanding of the mechanisms involved.

From the experimental side, reactive Mn(V)OP complexes were first generated at ambient temperature in water and spectroscopically characterized by Groves and co-workers.^{15,16} These species were found to unambiguously adopt a singlet ground state. On the basis of reactivity studies, Jin and Groves¹⁶ proposed that release of oxygen from Mn(V)OP⁺ should proceed via a thermally accessible reactive high-spin (triplet or quintet) state. Subsequently, Nam and co-workers^{17,18} and Newcomb and co-workers^{19,20} extended Groves' pioneering work. Nam and co-workers showed experimentally that the singlet state of [MnO(tcdpp)]⁺ (tcdpp = tetra-(2,6-dichlorophenyl)-porphyrin) was not capable of oxygenating alkanes and thus active species were predicted to be probably high spin. These findings suggested that the concept of two-state reactivity could be applied also to Mn(V)OP species, analogously to iron-oxo species.²¹ The authors also reported that manganese(V)-oxo porphyrins associated with terminal oxidants, such as PhIO, afforded relatively high product yields in the oxygenation of olefins (36-24%) and somewhat lower yields in the oxygenation of alkanes (10-16%), where equimolar amounts of alcohol and ketone products were observed. Such low product yields in the hydroxylation reactions These findings suggested that the concept of two-state reactivity could be applied also to Mn(V)OP species, analogously to iron-oxo species.²² and the prediction that a singlet ground state and thermally accessible higher spin states are likely involved

in the reaction with MnOP complexes are inconsistent. However, as we will show in the present work, this prediction is a key element of the solution of the conundrum.

Newcomb and co-workers²⁰ generated porphyrin-manganese(V)-oxo species from the corresponding manganese (III) perchlorate salts via laser flash photolysis (LFP), detecting the highly reactive Mn-oxo intermediates in organic solvents and performing direct kinetic studies of their reactions with typical organic substrates (*cis*-stilbene, Ph₂CH₂, PhEt, and PhEt-d₁₀). Three different porphyrins in the Mn-oxo complexes, namely 5,10,15,20-tetraphenylporphyrin (TPP), 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (TPFPFPP) and 5,10,15,20-tetrakis(4-methylpyridinium)porphyrin (TMPyP), were employed. Reactions of Mn(V)OP with the substrates are complicated because of the simultaneous presence under reaction conditions of Mn(III), Mn(IV) and Mn(V) species. indicated no formation of Mn(IV)OP and velocities of comproportionation reactions of Mn(V)OP with the Mn(III)P products from the oxidation of substrate smaller than the velocities of the reactions of Mn(V)OP with substrate. “Apparent” rate constants for reactions of Mn(IV)OP derivatives, produced photochemically from the corresponding manganese(III) chlorate salts, showed that these intermediates react very fast (with nearly a diffusion-controlled rate constant) via disproportionation to give Mn(V)OP and Mn(III)XP species, where X could be one of the counterions present in the photolysis conditions (Cl⁻, ClO₄⁻, ClO₃⁻, NO₃⁻) or hydroxide, and that Mn(V)OP was the major, or possibly the only, active oxidant in the reactions. The Mn(III)/Mn(IV)/Mn(V) equilibrium involved in the oxidation reactions was described as: 2HX + 2 Mn(IV)OP $\rightleftharpoons$ (Mn(V)OP)⁺ + Mn(III)XP + H₂O + X⁻. and the authors provided evidence that the velocities of disproportionation and comproportionation reactions can readily exceed the velocities of substrate oxidations. The apparent equilibrium constant values for the disproportionation reactions of Mn(IV)OP in CH₃CN as solvent indicated that little of the highly reactive Mn(V)OP species would be present in a catalytic reaction. The reactivity patterns determined from LFP studies of (TPFPFPP)Mn(V)O were also reproduced in the catalytic reactions using mcpba (meta-chloroperbenzoic acid) or iodosobenzene as sacrificial oxidant. The equilibrium between Mn(III)/Mn(IV)/Mn(V) species involved in the reaction was observed to serve to sequester much of the potential catalyst as unreactive Mn(IV)OP. Interestingly, in the Mn(IV)OP case, the measured rate constants for the formation of oxidized products could be apparent and much lower than the true rate constants for reaction of the active oxidants with substrates.

Later work by Groves and co-workers²³ found strongly pH dependent O-transfer reactivity for Mn(V)O TMP (TMP=tetramesitylporphyrin). At a high pH the oxo complex is unreactive, whereas at low pH O transfer takes place. This behavior was associated with acid-base equilibria involving three protonation states of the Mn(V)OP system, namely [MnOP(H₂O)]⁺, [MnOP(OH)] and [MnOPO]⁻.

Each of these species containing a different O-bound ligand trans to the oxo group was shown to have different reactivity.

Overall, the experimental results provide a picture of an unusual reactivity pattern exhibited by these MnOP species. They derive from three main effects: the spin-state crossing, the equilibration of different oxidation state species, Mn(V), Mn(III) and Mn(IV), and the pH dependence of the processes.

Generally, for metalloporphyrin-catalyzed oxidation of substrates, the so-called Groves rebound mechanism is widely accepted.^{24, 25, 26} It consists of three steps: 1) oxidation of the Mn(III)P (P=porphyrin) catalyst to Mn(V)OP oxo intermediate; 2) H atom abstraction from the substrate C-H bond, leading to an organic radical and a Mn(IV)OHP hydroxo intermediate; and 3) OH-rebound by OH transfer to the organic radical. The rate-determining step (RDS) is the H-abstraction step and the key intermediate is the Mn(V)OP oxo species.

A combined experimental/theoretical work by Brudvig, Crabtree, Eisenstein and co-workers¹² showed that a postulated Mn-oxo active species, [Mn(O)(tpp)(Cl)] (tpp = tetraphenylporphyrin), could promote the oxidation of DHP (DHP = 9,10-dihydrophenanthrene) by competitive desaturation and hydroxylation pathways, which share a common initial step, radical H abstraction from one of the DHP sp³ C-H bonds, leading to a product mixture. Interestingly, under various reaction conditions (i.e. in N₂ or air atmosphere, in CD₂Cl₂ or CD₃CN solvents) the hydroxylation yields were always lower than the desaturation yields (11-26 % and 46-67%, respectively in N₂, 9-11% and 2-31%, respectively, in air).

From the theoretical side, Nam et al. experimental findings¹⁸ were examined by Eisenstein and co-workers.²⁷ The authors carried out DFT investigations on the Groves rebound mechanism for the oxidation of toluene catalyzed by a model of [MnO(tdcpp)]⁺. In this work the singlet state of the oxo intermediate was shown not to be active, whereas the reaction could easily take place on the lowest lying triplet and quintet potential energy surfaces with very low energy barriers, in agreement with experimental results. In addition, it was demonstrated that the rebound mechanism for this reaction is favored for spin states with oxyl character.

A recent investigation on the Mn(V)OP⁺ system performed by Pierloot et al.²⁸ with correlated ab initio methods (CASPT2, RASPT2) provided an accurate description for the spin state energetics, the oxyl character of the complex and for their role in oxygen transfer reactions. Analogously, the Mn(V)OP⁺ singlet ground state was proven to lack the oxyl character and to be kinetically inert. As proposed by Jin and Groves,¹⁶ Pierloot and co-workers²⁸ demonstrated that the oxygen transfer from Mn(V)OP⁺ should proceed via a thermally accessible reactive high spin state (triplet or quintet) which provides sufficient oxyl character to the system for reacting. In particular, the triplet state has been shown to

correspond to the excitation of an electron from a non-bonding Mn 3d_{xy} orbital to one of the Mn=O π^* orbitals, thus giving rise to a certain amount of oxyl character.

Importantly, by the RASPT2 analysis it was also shown that in a density functional theory framework pure functionals have to be preferred over hybrid ones, since for these systems hybrid functionals yield less accurate energies and are extremely dependent on the contribution of exact exchange and hence, inadequate for quantitative reaction mechanism studies.

On the basis of Groves and co-workers' experimental results,²³ Groves and co-workers²⁹ and Eisenstein and co-workers³⁰ theoretically investigated the reactivity of Mn(V)OP species. These investigations both rationalized the fact that, experimentally, these compounds are less reactive under basic than under acidic conditions and provided a new perspective about Mn-oxo porphyrin reactivity based on the finding that the larger the low spin/high spin energy gap the less reactive the compound. In particular, the reactivity of the isomeric Mn(V)O(2-TMPyP) and Mn(V)O(4-TMPyP) (2-TMPyP = 2-tetra-N-methylpyridyl; 4-TMPyP = 2-tetra-N-methylpyridyl) species was investigated and results showed that both the basicity of the oxo ligand (proton affinity) and the low spin-high spin electron-promotion energy effects contribute to modulate their reactivity.²⁹ The H-abstraction process for the three protonation states of Mn(V)OP, namely [MnOP(H₂O)]⁺, [MnOP(OH)] and [MnOPO]⁻, was studied, confirming that the lowest trans-influence ligand, H₂O, gives the most reactive complex.³⁰ The reactivity was found to increase along the series in the order O²⁻ < OH⁻ < H₂O, in agreement with the experimentally observed pH effect on MnOP reactivity.²³ Generally, the theoretical results point out that in the Mn(V)OP-catalyzed hydroxylation reaction mechanism the rate-determining-step is the H-abstraction step and that a reasonable activation barrier is the spin-crossover, characterized as an instantaneous transition from a singlet to a thermally accessible triplet spin state of the Mn(V)OP complex before it reacts. In this framework, these Mn(V)OP species are depicted as good candidates for substrate oxidations even at thermal conditions and the free energy barrier was estimated roughly as 10-15 kcal/mol.²⁷ However, in the work of Brudvig, Crabtree, Eisenstein and co-workers,¹² as well as in Nam and co-workers experiments,¹⁸ the yield of hydroxylated product is inconsistently low. These experimental data might suggest that the hydroxylation rate constant is low and thus the rate determining step free energy barrier is very high, in clear contradiction to theoretical results. We should note that the solution conditions in which these kinetics were carried out are quite complicated, since many equilibria could be involved. First of all the Mn species, *inside the pot*, show different oxidation states (Mn(III), Mn(IV), Mn(V) porphyrin complexes are present) which can have different oxidation powers, as observed in Newcomb and co-workers work.²⁰

Thus, the question arises as to how to reconcile the computational picture of Mn(V)OP species as very reactive intermediates, with thermally accessible spin-crossover reaction barriers, with the

experimental evidence that MnOP complexes show very low yields in hydroxylation reactions, implying low rate constants and high reaction barriers.

The resolution of this conundrum is very important to improve the catalytic conditions and it certainly deserves further studies. This is the aim of this work. Here, we use toluene hydroxylation by $\text{Mn(V)OP(H}_2\text{O)}^+$ complex to gain a deep insight into the reaction mechanism and to provide a rationale of Newcomb and co-workers experimental data.²⁰ Based on their fundamental kinetic studies, in our analysis we will focus only on the Mn(V) species since, although the Mn(V)OP intermediate is actually not highly concentrated in a catalytic reaction and is present in equilibrium with Mn(III) and Mn(IV) species, it is considered as the only active oxidant. The H-abstraction from toluene by $\text{Mn(V)OP(H}_2\text{O)}^+$ is depicted in Scheme 1. In this spin-forbidden process the spin state changes from singlet in the reactants to triplet in the products. Firstly, the reaction profile is calculated using the minimum energy crossing point (MECP) approach which suggests that the process should occur through a preliminary spin-crossover in the $\text{Mn(V)OP(H}_2\text{O)}^+$ complex from singlet to triplet and a subsequent H-abstraction from toluene with a very low activation barrier, in agreement with literature theoretical studies. Then, the singlet-triplet energy gap for the $\text{Mn(V)OP(H}_2\text{O)}^+$ complex is calculated at the DFT/BP86 level of theory and a validation of the employed functional against the high-level correlated DMRG-CASPT2/CC method³¹ is performed to estimate the error bars of our results. DFT failures, associated with the description of relative energies of different spin states and their functional dependence, have been widely illustrated in the literature.³² Successively, as far as the low spin/high spin crossing is the rate determining step of this reaction, we study the influence of different experimental conditions on the spin-crossover barrier and, finally, we propose a simplified model for the whole process mechanism and we compare the calculated activation Gibbs free energy to high resolution kinetics data provided by Newcomb and co-workers.²⁰ **Error! Bookmark not defined.** The results of this work will deliver the resolution of the apparent conundrum.

Scheme 1: Schematic representation of H-abstraction process $\text{MnOP}(\text{H}_2\text{O})^+ + \text{C}_6\text{H}_5\text{CH}_3$ studied in this work.

Computational details

DFT calculations

DFT calculations were performed in the gas phase with the ADF 2014.04 program package,³³ employing a BP86 functional,³⁴ Grimme3 BJ damping dispersion corrections (DFT-D3-BJ),³⁵ a Slater-type TZ2P quality basis set and a scalar ZORA Hamiltonian to include relativistic effects.³⁶ The computation of the minimum energy crossing points (MECP) was carried out using a program developed by J.N. Harvey³⁷ and interfaced with the ADF package, with the computational details described above. Activation free energy barriers $\Delta G^\ddagger$ were calculated by means of analytical frequencies. The gas-phase $\Delta G^\ddagger$ was computed as the sum of $\Delta H^\ddagger$ and $-T\Delta S^\ddagger$ at 298.15 K.

DMRG-CASPT2/CC calculations

A recently proposed approach, referred to as DMRG-CASPT2/CC,³¹ was employed in order to examine the reliability of the BP86 functional for the energetic description of the $\text{MnOP}(\text{H}_2\text{O})^+$ singlet/triplet energy gap. In this approach, DMRG-CASPT2 was used to describe valence electron correlation, whereas semicore (Mn 3s3p) electron correlation was described with low-cost coupled cluster CCSD(T). The active space consists of 16 orbitals for the singlet state, $^1\text{MnOP}(\text{H}_2\text{O})^+$, and 17 orbitals for the triplet state, $^3\text{MnOP}(\text{H}_2\text{O})^+$. This active space was built in order to account for the static correlation of the Mn 3d shell, the covalency of the Mn=O bond and the σ donation from the porphyrin, by including four pairs of the following bonding/antibonding molecular orbitals: Mn ($3d_{z^2}$)-O($2p_z$) (σ_z, σ_z^*), Mn ($3d_{xz}$)-O($2p_x$) (π_{xz}, π_{xz}^*), Mn ($3d_{yz}$)-O($2p_y$) (π_{yz}, π_{yz}^*) and Mn ($3d_{xy}$)-P(σ_{xy}) ($\sigma_{xy}, \sigma_{xy}^*$). We also included the non-bonding Mn($3d_{xy}$) orbital and four additional π orbitals on the porphyrin known as the Gouterman set containing two high-lying occupied π orbitals, P (πa_{1u}) and P (πa_{2u}), and the correlating P (π^*_{eg}) orbitals. Finally, we modelled the so-called ‘double-shell’ effect of Mn and O by adding two oxygen orbitals ($3p_x$ and $3p_y$) and one/two Mn($4d$) orbitals for $^1\text{MnOP}(\text{H}_2\text{O})^+ / ^3\text{MnOP}(\text{H}_2\text{O})^+$, respectively.

DMRG-CASPT2 calculations were carried out using the CheMPS2 code³⁸ interfaced with the program OpenMolcas.³⁹ The number of renormalized states (m) is 2000. An ANO-RCC type basis set was used with the following contractions: [7s6p5d3f2g1h] for the metal atom;⁴⁰ [4s3p2d1f] for O, C and N;⁴¹ and [3s1p] for H.⁴² To lower the computational cost, we employed the Cholesky decomposition technique for the two electron integrals⁴³ with a threshold of 10^{-6} au. Scalar relativistic effects were taken into account with a standard second-order Douglas-Kroll-Hess (DKH) Hamiltonian.⁴⁴

In all PT2 calculations, we used the standard ionization potential electron affinity (IPEA) shift of 0.25 au.⁴⁵ An imaginary shift of 0.1 au was applied in order to prevent weak intruder states and improve convergence.⁴⁶ Manganese (3s3p) correlation was described with the partially spin-restricted coupled cluster RCCSD(T) method as implemented in Molpro v.2012.⁴⁷ The basis set was aug-cc-pwCVTZ-DK for Mn⁴⁸ and MINAO for the remaining atoms.⁴⁹

Results and Discussion

Reactivity of $\text{MnOP}(\text{H}_2\text{O})^+$ with toluene: H-abstraction process

To explore the H-abstraction reactivity, we calculated a reaction profile using the MECF approach. It is depicted in Figure 1. The singlet reactant complex ^1RC is stabilized by -6.5 kcal/mol with respect to the separated reactants. The MECF is placed at the beginning of the reaction and it represents the rate-determining-step (RDS) for this process with a low activation barrier ($\Delta E_{\text{spin-cross}}^\ddagger$) of 3.7 kcal/mol. Thus the MECF is thermally accessible by the system since only 3.7 kcal/mol are needed to access the triplet PES within the accuracy of the BP86 functional. Then the triplet reactant complex ^3RC is formed and the substrate H atom is abstracted via a transition state located on the triplet PES (^3TS) at only 0.5 kcal/mol ($\Delta E_{\text{abstraction}}^\ddagger$) above the triplet reactant complex ^3RC .

Figure 1: Reaction profile for the H-abstraction from toluene by $\text{MnOP}(\text{H}_2\text{O})^+$.

On comparing the O-H distance between the hydrogen of the methyl group of toluene and the oxo group of the catalyst we observe a large distance (2.024 Å) in the singlet reactant complex ^1RC and a reduced distance (1.787 Å) in the MECP structure which is close to that (1.668 Å) in the triplet reactant complex ^3RC . These findings suggest that the process should occur through a preliminary spin-crossover taking place on the $\text{MnOP}(\text{H}_2\text{O})^+$ complex from singlet to triplet and a subsequent H-abstraction of the toluene hydrogen with a very low activation barrier of 0.5 kcal/mol, promoted by the oxyl character of the triplet Mn-oxo-porphyrin complex.

Due to the importance of the spin-crossover on the Mn-oxo-porphyrin complex, it is interesting to compare the $\text{MnOP}(\text{H}_2\text{O})^+$ optimized geometry for the singlet and triplet spin states. The structures are reported in Figure 2.

Figure 2: MnOP(H₂O)⁺ structure optimized in the singlet (left panel) and triplet (right panel) spin states. Distances are in Å.

1.588 Å, and a consequent shortening of the Mn-OH₂ one, from 2.377 to 2.314 Å, from singlet to triplet state. The Mn distance from the plane of the nitrogen atoms, defined as the distance between Mn and the centre of mass of the four N atoms shortens from 0.331 in the singlet to 0.249 Å in the triplet.

The porphyrin equatorial ligand is also dramatically affected by the spin state change, with the major change being an enhancement of the ruffling distortion. Both the MnOP(H₂O)⁺ singlet and triplet structures are found in a ruffling conformation which can be measured by a ruffling dihedral angle relating to the positions of four carbons atom located at the bottom of two opposite pyrroles (see Figure S1 in the SI). The ruffling can be envisaged as twisting along the Mn-N(pyrrole) bonds in alternate directions, resulting in an out-of-plane distortion for the porphyrin. The ruffling dihedral angle increases from 18.0° in the singlet to 37.1° in the triplet, thus indicating that the spin state change in the complex significantly affects the conformation of the porphyrin ligand. The ruffling distortion of the system under study is analogous to the one experienced by the biochemically relevant heme group.⁵⁰ It has been recently demonstrated, by employing the simplified model of bis-imidazole-coordinate Fe porphyrins, that the ruffling distortion reduces the redox potential of heme, making it a more effective oxidant.⁴⁹

The singlet-triplet energy difference for the MnOP(H₂O)⁺ complex is calculated to amount to 6.5 kcal/mol, with the singlet as the ground spin state. These findings are in complete agreement with previous results from ref. 30, where three different spin states, the singlet, triplet and quintet, were computed for [MnO(tHp)(H₂O)]⁺ (tHp = tetrahydrogenporphyrin), with the singlet being the ground state and the triplet and quintet states lying 4.7 and 12.1 kcal/mol, respectively, above the singlet. The structural variation trend is also reproduced, with the Mn=O distance elongating from singlet (1.55 Å) to triplet (1.61 Å) and quintet (1.68 Å) and the Mn-OH₂ bond shortening from singlet (2.22 Å) to triplet (2.17 Å) and quintet (2.16 Å).³⁰

Validation of the computational approach: DFT vs DMRG-CASPT2/CC

In order to have an idea on the reliability of the BP86 functional for the evaluation of the spin-crossover energy barrier we performed single point DMRG-CASPT2/CC calculations on the two spin states, singlet and triplet, of the $\text{MnOP}(\text{H}_2\text{O})^+$ complex and we compared their gap value with the one provided by BP86. It has been shown that DMRG-CASPT2/CC is capable of providing accurate spin state energetics of the first-row transition metal compounds with an error of a few kcal/mol.³¹

The $\text{MnO}(\text{H}_2\text{O})^+$ porphyrin geometries employed for these single point calculations were optimized with our previously described computational set up in a C_s symmetry. The singlet-triplet energy difference predicted by the BP86 functional is now 6.8 kcal/mol (6.5 kcal/mol without symmetry constraint). DMRG-CASPT2 with only valence electrons correlated gives a singlet-triplet energy difference of 3.3 kcal/mol. In agreement with previous works,³¹ (3s3p) electron correlation calculated with CCSD(T) favors the low-spin over high-spin state (by 1.7 kcal/mol). The final energy gap between singlet and triplet predicted by DMRG-CASPT2/CC is estimated to be 4.9 kcal/mol. We could state that the energy description of the spin states provided by the BP86 functional is (6.8 kcal/mol) in good agreement with the DMRG-CASPT2/CC one and, thus, it is accurate for the modeling of the system.

Interestingly, the orbitals occupation numbers of the CASSCF calculation provide evidence that the main contribution to the triplet wavefunction arises from a configuration in which an electron is excited from a Mn $3d_{xy}$ orbital to a Mn-oxo π^* one (see Figure S2 in the SI). This explains the elongation of the Mn-oxo distance in the triplet state complex, since a non-bonding electron is promoted to an anti-bonding Mn-oxo orbital and clarifies the fact that, for the triplet, the main charge transfer contributions comes from the metal center and not from the porphyrin ligand.

All these results are in good agreement with those found by Pierloot and co-workers²⁸ for a Mn(V)-oxo-porphyrin system without any axial ligand. Here we find that the introduction of the water in trans position to Mn(V)-oxo group does not change the electronic configuration of the spin state, it solely contributes to lower the singlet-triplet energy gap (5.6 kcal/mol in ref. 28 vs. 4.9 kcal/mol in this work).

Axial ligand influence on reactivity

Highlighting how the different solution conditions influence the reactivity of the Mn-oxo porphyrin complex is very important to improve its catalytic efficiency. The presence in solution of species like ions, solvent molecules or base able to coordinate to the Mn atom could have an impact on the catalyst reactivity.

The role of the acidity on the reactivity of Mn-porphyrin has been experimentally reported by Groves and co-workers,²³ and it was theoretically studied by Groves and co-workers²⁹ and later on by Eisenstein and co-workers.³⁰ Eisenstein and co-workers showed that different axial ligands, modeling the pH-dependent Mn-oxo porphyrin reactivity, namely H₂O at low pH, OH⁻ at intermediate pH and O²⁻ at high pH values, change the reactivity of the catalyst. Based on literature results,³⁰ we also propose here that the reactivity of the Mn-oxo porphyrin complex is tuned by the singlet/triplet energy gap, with smaller gaps corresponding to more reactive complexes. Thus we carried out several geometry optimizations by replacing the axial water with different X ligands (specifically X = OH⁻, O²⁻, CH₃CN, Cl⁻ and none) to investigate how the singlet-triplet energy gap is quantitatively influenced.

From a geometrical perspective, we have found that the influence provided by the axial ligands is driven by both their basicity and charge. The Mn=O distance has been found to change in the order none $\approx$ CH₃CN $\approx$ H₂O < Cl⁻ $\approx$ OH⁻ < O²⁻ in both the singlet and triplet spin states (see Figure S3 in the SI).

As we could expect, the Mn=O distance increases with the basicity of the axial ligand, whereas it appears to be much less affected by the charge of the ligand. Interestingly, in the case of OH⁻ and Cl⁻, the Mn=O bond is not orthogonal to the porphyrin plane (the angle in these cases changes from 90 to about 85 degrees) (see Figure S4 in the SI). The same trend, although in the reverse order (decreasing with basicity), has been observed for the ruffling dihedral angle of the porphyrin in both the singlet and triplet spin states: O²⁻ < OH⁻ $\approx$ Cl⁻ < CH₃CN $\approx$ H₂O $\approx$ none (see Figure S5 in the SI).

Interestingly, in the case of the O²⁻ ligand the porphyrin is flat in both the two different spin states, whereas for OH⁻ and Cl⁻ it is flat in the singlet state and it is ruffled by 21.1-22.0° in the triplet state. For H₂O, CH₃CN and the bare complex (none) the porphyrin is ruffled by 36.4-37.1° in the triplet state, and it shows different values of the ruffling dihedral angle in the singlet state (18.0, 7.4 and 27.0°, respectively) (see Figure S5 in the SI). Generally, in the triplet spin state the porphyrin ruffling is significantly larger than in the singlet state for all the considered ligands, thus suggesting that the ruffling distortion might be associated with an enhanced reactivity, analogously to what it has been found for the heme group.⁵⁰

Finally, the Mn-X distance follows the trend $\text{O}^{2-} < \text{OH}^- < \text{Cl}^- < \text{CH}_3\text{CN} \approx \text{H}_2\text{O}$ in the singlet state and $\text{O}^{2-} < \text{OH}^- < \text{CH}_3\text{CN} < \text{H}_2\text{O} \approx \text{Cl}^-$ in the triplet spin state, as shown in Figure S6 in the SI. Generally we observe that the Mn-X distances are larger for the triplet than for the singlet state, apart from water and acetonitrile where this trend is reversed (Figure S6), and that they are mostly tuned by the basicity of the axial ligand rather than by its charge.

Table S1 in the SI summarizes for each species the most important geometrical parameters and the energy gap between singlet and triplet states.

We find that the singlet-triplet gap increases along the series Cl^- (5.7 kcal/mol) < H_2O (6.5 kcal/mol) < none (9.8 kcal/mol) $\approx \text{OH}^-$ (9.8 kcal/mol) < CH_3CN (10.2 kcal/mol) $\ll \text{O}^{2-}$ (28.4 kcal/mol), with O^{2-} yielding a much larger gap than all the other ligands. Notably no correlation can be found between structural data and the $[\text{MnOP}(\text{X})]^+$ singlet-triplet energy gap.

On the other hand, the reactivity has been previously reported to be entirely controlled by the large increase in the singlet-triplet gap caused by high trans influence ligands by Eisenstein and co-workers³⁰ and Groves and co-workers²⁹ for Mn-catalyzed C-H and bromide oxidation, respectively, where $\text{X} = \text{H}_2\text{O}$, OH^- and O^{2-} . Thus, the reactivity trend we calculate here in the C-H oxidation of toluene could be rationalized in terms of the electronic structure of the $[\text{MnOP}(\text{X})]^+$ intermediates. Frontier molecular orbital diagrams of all the $[\text{MnOP}(\text{X})]^+$ complexes are provided in Figure 3.

Figure 3: Frontier molecular orbitals for the singlet state of $[\text{MnOP}(\text{X})]^+$ ($\text{X} = \text{none}, \text{CH}_3\text{CN}, \text{Cl}^-, \text{H}_2\text{O}, \text{OH}^-, \text{O}^{2-}$) complex series. Orbitals involved in the electron promotion leading to the triplet state are in red color. Energy difference between these orbitals is also reported (in eV). Labels for π^* orbitals indicate the presence (X-Mn=O) or the absence (Mn=O) of contribution from the axial ligand.

In the singlet ground state the two 3d electrons of the Mn(V) center are paired in one nonbonding $3d_{xy}$ -like MO ($3d_{xy}$). The Mn-O σ bond arises from bonding/antibonding combinations of Mn d_{z^2} and O p_z (σ, σ^*) and a double π bond is formed from bonding/antibonding MO pairs between Mn (d_{xz}, d_{yz}) and O(p_x, p_y) ($\pi_{xz}, \pi_{yz}, \pi_{xz}^*, \pi_{yz}^*$), with different axial ligand participation (X-Mn=O). The three bonding combinations σ, π_{xz} , and π_{yz} (not shown in Figure 3) are fully occupied, whereas the corresponding antibonding MOs σ^*, π_{xz}^* , and π_{yz}^* remain empty, giving rise to a triple Mn-O bond lacking oxygen radical character. For all the complexes, except $[\text{MnOP}(\text{O})]^-$, the HOMOs are the two π orbitals of the porphyrin ligand which are close in energy and are located above the doubly occupied Mn d_{xy} , which represents instead the HOMO in the case $\text{X}=\text{O}^{2-}$. The LUMOs are the two almost degenerate π^* (Mn=O) orbitals (π_{xz}^* and π_{yz}^*), which can raise their energies by antibonding mixing with the axial ligand. For $\text{X} = \text{O}^{2-}$ having a high trans influence, the energy of the π^* (O=Mn=O) orbitals is increased, and they locate above the two π^* orbitals of the porphyrin which become the LUMOs. Interestingly, the axial H_2O and CH_3CN ligands do not mix with the π^* (Mn=O). In the case of H_2O , the lone pair is far removed in energy from the π^* (Mn=O) orbital and therefore does not overlap with the metal d orbitals. For OH^- , instead, the lone pairs are more diffuse and close in energy to π^* (Mn=O), thus favoring the overlap with the Mn d orbitals. As a consequence, the axial OH^- ligand participates in the π interactions of the HO-Mn=O moiety which raises in energy the π^* orbitals (HO-Mn=O). Analogously, the fully occupied p_x and p_y nonbonding combinations of the axial Cl^- ligand overlap with Mn d orbitals, thus participating in the π^* orbitals (Cl-Mn=O) and pushing them up in energy (although to a lesser extent than the axial OH^-). In the case of O^{2-} , the overlap between the metal d orbitals and the fully occupied p_x and p_y orbitals of the trans oxygens is large. Consequently, the strong involvement of both oxygens in the π^* orbitals (O=Mn=O) increases their energy substantially. The triplet state for all of the complexes invariably arises from the promotion of one electron from the doubly occupied Mn $3d_{xy}$ orbital to one of the antibonding π^* (X-M=O) orbitals, which becomes singly occupied. These orbitals are depicted in Figure S7 in the SI for all the complexes. This explains the weakening of the Mn=O bond and the gain in oxyl character in the triplet state. According to ref. 30, the singlet-triplet energy gap is mainly determined by the energy of these orbitals. In Figure 3 the Mn $3d_{xy} - \pi^*$ (X-M=O) energy gap is shown for all the different

ligands. The trend reported by Eisenstein and co-workers³⁰ for the axial ligand series $X = \text{H}_2\text{O}$, OH^- and O^{2-} is well reproduced, and a good correlation between the singlet/triplet energy gaps and the $\text{Mn } 3d_{xy} - \pi^* (X\text{-M=O})$ energy differences is found within the entire series of axial ligands, as shown in Figure 4.

Figure 4: Correlation plot between singlet/triplet energy gap ($\Delta E_{S/T}$) (kcal/mol) and $\text{Mn } 3d_{xy} - \pi^* (X\text{-M=O})$ energy difference ($\Delta E(d_{xy} - \pi^*)$) (eV) for all the $[\text{MnOP}(X)]^+$ ($X = \text{none}, \text{CH}_3\text{CN}, \text{Cl}^-, \text{H}_2\text{O}, \text{OH}^-, \text{O}^{2-}$) complex series ($R^2 = 0.9463$).

These results confirm the finding that the reactivity (and then the singlet/triplet energy gap) is mainly controlled by the axial ligand trans influence.³⁰

The $\pi^* (X\text{-M=O})$ orbitals are key for reactivity since they act as electron acceptors for the C-H bond breaking (“ π -channel reactivity”). Generally speaking, the lower the acceptor orbital lies in energy and the higher the oxo oxygen contribution is, the more electrophilic the Mn(V)O moiety will be. From a ligand-field perspective, on the basis of our results, we can observe that i) the spin state (both singlet and triplet) in the $[\text{MnOP}(X)]^+$ complex series is determined by the nature of the equatorial ligands (P) alone, irrespective of the nature of the axial ligand; ii) the triplet state is the reactive state in contrast to the singlet in hydrogen abstraction; iii) the reactivity of the triplet is driven by transfer of an electron to a low-lying π^* orbital; and iv) the axial ligand (X) regulates the reactivity of the complex by inducing relatively minor shifts in the energy of the lowest-lying π^* orbital through $X - \text{Mn=O } \pi$ antibonding interactions. An indirect axial ligand effect arises from charge build up, that is ligands donating electron charge to the metal center, which will decrease the positive charge on the

metal and the Mn-oxo group. Positive charge on that group is important for the lowering of the barrier to H abstraction, since it lowers the energy of the electron acceptor orbital. Charge exerts a strong effect, when charged ligands are considered: negative charge (for instance O^{2-}) sizably increases the energy of the π^* acceptor orbital, in agreement with the trend of decreasing reactivity with increasing electron donation ($H_2O > OH^- > O^{2-}$). These ligand field effects have been further tested with additional calculations for different axial ligands ($X = CN^-$, ClO_3^- , NO_3^- , NH_3 and SCN^-) which confirm the previous findings. Results concerning geometries and energies are reported in Tables S2 and S3 the SI. Analogously, the triplet state for all of the additional complexes arises from the promotion of one electron from the doubly occupied Mn $3d_{xy}$ orbital to one of the antibonding π^* ($X-M=O$) orbitals, which is responsible for the weakening of the Mn=O bond and the gain in oxyl character in the triplet state. The singlet-triplet gap trend along the whole ligand series is now modified as follows: SCN^- (S-bonded) (3.8 kcal/mol) < NO_3^- (4.8 kcal/mol) < CN^- (4.9 kcal/mol) < Cl^- (5.7 kcal/mol) < ClO_3^- (5.8 kcal/mol) < H_2O (6.5 kcal/mol) < none (9.8 kcal/mol) $\approx$ OH^- (9.8 kcal/mol) < CH_3CN (10.2 kcal/mol) < NH_3 (10.7 kcal/mol) $\ll$ O^{2-} (28.4 kcal/mol), with the doubly negative O^{2-} yielding again a much larger gap than all the other ligands.

However, when comparing ligands with similarly small trans influence in complexes with the same +1 charge, namely $X = H_2O$, CH_3CN , and none, the correlation between the singlet/triplet energy gaps and the Mn $3d_{xy}$ - π^* ($X-M=O$) energy differences is lost. Indeed, within this ligand subset the largest singlet/triplet energy gap is calculated for CH_3CN which shows a Mn $3d_{xy}$ - π^* ($M=O$) energy difference very close to that calculated for H_2O (1.14 vs. 1.16 eV, respectively) and smaller than that of $X=none$ (1.29 eV). This finding suggests that other factors than trans influence might tune the reactivity. One factor could be the porphyrin ruffling distortion, which is surprisingly small in $[MnOP(CH_3CN)]^+$ (RDA = 7.4°), larger in the $[MnOP(H_2O)]^+$ (RDA = 17.9°), and the largest in the $[MnOP]^+$ (RDA = 27.0°) singlet state. In Figure 5 the Mn $3d_{xy}$ and π^* ($M=O$) orbitals for $X = none$, H_2O and CH_3CN are shown in more detail.

Figure 5: Mn 3d_{xy} and π^* (M=O) molecular orbitals for the singlet state of [MnOP(X)]⁺ (X = none, CH₃CN, H₂O) complex subset. Ruffling dihedral angles (RDA) (in degrees) and orbital energies values (in eV) are also reported.

On comparing X=none and X = H₂O, we see that the Mn 3d_{xy} - π^* (M=O) energy difference (1.29 vs. 1.16 eV, respectively) is entirely due to Mn 3d_{xy} destabilization arising from antibonding mixing with porphyrin for X = H₂O (-9.51 vs. -9.40 eV, respectively), accounting for $\Delta E_{S/T}$ decreasing in [MnOP(H₂O)]⁺ (6.5 vs. 9.8 kcal/mol, respectively). Thus, the porphyrin ruffling effect should be that of stabilizing the singlet ground state, enhancing the singlet/triplet gap and making the system less reactive. This effect can be also seen for the almost flat X = CH₃CN, where the Mn 3d_{xy} destabilization is even higher (-9.51 vs. -9.14 eV, respectively). On this basis we could estimate a Mn 3d_{xy} - π^* (M=O) energy difference of about 0.92 eV and a decreased $\Delta E_{S/T}$ in [MnOP(CH₃CN)]⁺ which is not observed (10.2 kcal/mol). Actually, we note that the porphyrin ruffling also affects the energy of π^* (M=O) orbitals, which are analogously stabilized with respect to the “flat” conformation (compare the π^* energy for X = none, -8.22 eV to that for X = CH₃CN, -8.00 eV). The π^* destabilization in “flat” [MnOP(CH₃CN)]⁺ accounts for 0.22 eV which sums up to the 0.92 eV estimate of the Mn 3d_{xy}

- π^* (M=O) energy difference, leading to the calculated 1.14 eV value. From these considerations the singlet ground state of $[\text{MnOP}(\text{CH}_3\text{CN})]^+$ should be the least stable and the smallest $\Delta E_{S/T}$ should be expected in the ligand subset. However, in the triplet state a porphyrin ruffling of the same amount is observed in all the complexes: $[\text{MnOP}]^+$ (RDA = 37.0°), $[\text{MnOP}(\text{H}_2\text{O})]^+$ (RDA = 37.1°), and $[\text{MnOP}(\text{CH}_3\text{CN})]^+$ (RDA = 36.4°), with X = CH₃CN experiencing the largest porphyrin conformation variation (ΔRDA = 29.0°). Thus, we might surmise that for X = CH₃CN the largest $\Delta E_{S/T}$ could be ascribed to an even less stable triplet, arising from the porphyrin ruffling. Then, within this ligand subset, the porphyrin conformational variation occurring from singlet to triplet does not allow to correlate the $\Delta E_{S/T}$ with the Mn 3d_{xy} - π^* (M=O) energy difference in the singlet. To further explore the idea that ruffling distortion could influence the reactivity, additional calculations have been performed by fixing the conformation of the porphyrin ligand to that observed for X=none (RDA = 27.0° in the singlet and 37.0° in the triplet) and varying the axial ligands (X = H₂O, CH₃CN) and spin states (singlet and triplet). Results are shown in Table S4 in the SI. Interestingly, although the singlet/triplet energy gap $\Delta E_{S/T}$ value changes only slightly from the previously calculated one by complete structure optimization (6.2 vs. 6.5 kcal/mol for H₂O and 10.7 vs. 10.2 kcal/mol for CH₃CN), the Mn 3d_{xy} - π^* (M=O) energy difference in the singlet state does change significantly (1.31 vs. 1.16 eV for H₂O and 1.30 vs. 1.14 eV for CH₃CN; note that for X=none the value is 1.29 eV). These very close Mn 3d_{xy} - π^* (M=O) energy difference values calculated for X=none, H₂O and CH₃CN in the singlet state suggest that they mainly account for porphyrin ruffling. Interestingly, the Mn 3d_{xy} - π^* (M=O) energy difference change from the fully optimized to the “ruffled” singlet for H₂O and CH₃CN is mainly due to the variation in the energy of the π^* (M=O) orbitals, which are now destabilized with respect to the fully optimized porphyrin conformation (-8.10 vs. -8.24 eV for H₂O and -7.80 vs. -8.00 eV for CH₃CN). On the contrary, the energy of the Mn 3d_{xy} orbital changes only slightly (-9.41 vs. -9.40 eV for H₂O and -9.10 vs. -9.14 eV for CH₃CN), indicating that they are more influenced by the axial ligand field effects. Thus, the porphyrin ruffling in the singlet state appears to mainly affect the energy of the π^* (M=O) orbitals, by pushing them up in energy (X=none, π^* energy = -8.22 eV; X = H₂O, π^* energy = -8.10 eV; X = CH₃CN, π^* energy = -7.80 eV). On this basis, we could expect that the “ruffled” triplet state arising from the promotion of one electron into the π^* orbitals would be more destabilized for CH₃CN than for H₂O, in agreement with the corresponding $\Delta E_{S/T}$ values. Similar reactivity tuning by porphyrin ruffling distortion could be expected for CN⁻, ClO₃⁻, NO₃⁻ and NH₃ axial ligands, whose complexes show a nearly “flat” porphyrin conformation in the singlet state (RDA values in the range 0.3-6.6°) and a significantly ruffled one in the triplet (RDA values in the range 35.2-23.4°) (see Table S2).

Our results show that, although the reactivity is mainly modulated by trans influence ligands, the porphyrin ruffling also finely tunes it, with CH₃CN giving the lowest reactivity within the X = none, H₂O, CH₃CN subset of comparable low trans influence ligands. These findings are corroborated by the spin density plots in the triplet state reported in Figure S8 in the SI for all the complexes. Only for X = Cl⁻, OH⁻, and O²⁻ species spin density partially localizes on the axial ligand, whereas only for X = H₂O, CH₃CN, and none partial spin density can be observed on the porphyrin moiety, interestingly located on the neuralgic points for the ligand ruffling folding.

In conclusion of this study, apart from the case of O²⁻, the singlet-triplet gap remains in the range of about 6 – 10 kcal/mol, thus the Mn-porphyrin complexes are expected to be reactive intermediates in the different conditions provided by different axial ligands. We could surmise that the compound becomes unreactive only in the case of strongly basic ligands, such as O²⁻. Interestingly, we have found that the charge of the ligand tunes the ruffling distortion of the porphyrin and that in the triplet the porphyrin is always remarkably more ruffled than in the singlet spin state. The dianionic and strongly basic O²⁻ axial ligand shows a flat conformation of the porphyrin in both singlet and triplet states.

A simplified model for Mn-porphyrin hydroxylation mechanism

As we pointed out in the Introduction, there is an apparent conundrum because our calculations suggest that the MnOP are very reactive intermediates, with low reaction barriers, whereas the Newcomb experiments²⁰ show that these complexes lead to very low yields in hydroxylation reactions, implying low rate constants and high reaction barriers. Basically the Mn(V) species, which are suggested to be the only one capable of high reactivity in catalytic conditions, are not highly concentrated, since they form Mn(IV) and Mn(III) intermediates that limit their amount. Thus, the measured rate constant could be apparent and lower than the real one.

This remark may clarify the incongruent result we found and will probably help to find new synthetic strategies to increase the experimental rate constant for the formation of oxidized products.

In order to have a quantitative idea of the agreement between our (and literature) theoretical studies and Newcomb kinetics²⁰ we propose, in this section a comparison between the DFT computed reaction barrier and the experimental one, by means of a simplified reaction model.

In the reactivity section we found that the MnOP(H₂O)⁺ complex reaction with the toluene substrate takes place *via* a first promotion from a low spin (singlet) to a high spin (triplet) state of the Mn-porphyrin, that it is a thermal process ($\Delta E_{S/T}^{\ddagger} = 6.5$ kcal/mol) and a rapid reaction of the excited complex with the substrate, which has a very low energy barrier ($\Delta E_{\text{abstraction}}^{\ddagger} = 0.5$ kcal/mol), to form

the final hydroxylated product occurs (Figure 1). Similar results were found by Eisenstein and co-workers³⁰ for $[\text{MnO}(\text{tHp})(\text{H}_2\text{O})]^+$ ($\Delta E_{\text{S/T}}^\ddagger = 4.7$ kcal/mol and $\Delta E_{\text{abstraction}}^\ddagger = 0.4$ kcal/mol), $[\text{MnO}(\text{tHp})(\text{OH})]$ ($\Delta E_{\text{S/T}}^\ddagger = 9.2$ kcal/mol and $\Delta E_{\text{abstraction}}^\ddagger = 4.3$ kcal/mol), and $[\text{MnO}(\text{tHp})(\text{O})]^-$ ($\Delta E_{\text{S/T}}^\ddagger = 27.3$ kcal/mol and $\Delta E_{\text{abstraction}}^\ddagger = 8.0$ kcal/mol). Although both $\Delta E_{\text{abstraction}}^\ddagger$ and $\Delta E_{\text{S/T}}^\ddagger$ values depend on the axial ligand, their relative values remain constant within each complex, where $\Delta E_{\text{abstraction}}^\ddagger$ is always much smaller than $\Delta E_{\text{S/T}}^\ddagger$.

These results are now summarized in Scheme 2.

Scheme 2: Simplified scheme of the $\text{MnOP}(\text{H}_2\text{O})^+ + \text{toluene}$ H-abstraction reaction

This reaction profile allows us to propose a simplified stepwise model for the reaction composed by a pre-equilibrium and a virtually barrier-less reaction. A first equilibrium between the singlet and the triplet Mn(V)OP complex (reac. 1) and a second irreversible reaction of the latter with toluene or other organic substrate (reac. 2) are defined as:

We derive the kinetics law for the formation of the hydroxylated product P and we arrange the expression in terms of $\Delta G^\ddagger$, free Gibbs energy barrier for reac. 2, and ΔG° , standard free Gibbs energy for the equilibrium in reac. 1.⁵¹ To this aim we use the Eyring formula as follows:

$$\frac{d[P]}{dt} = k_2 \cdot [{}^3\text{MnOP}][\text{substrate}] = k_2 \cdot K \cdot [{}^1\text{MnOP}][\text{substrate}]$$

$$\frac{d[P]}{dt} = \frac{kK_B T}{h} \cdot \exp\left(\frac{-\Delta G^\ddagger}{RT}\right) \cdot \exp\left(\frac{-\Delta G^\circ}{RT}\right) \cdot [{}^1\text{MnOP}][\text{substrate}]$$

$$\frac{d[P]}{dt} = \frac{kK_B T}{h} \cdot \exp\left(\frac{-\Delta G^\ddagger + \Delta G^\circ}{RT}\right) \cdot [{}^1\text{MnOP}][\text{substrate}]$$

This final expression suggests that, in such a case of pre-equilibrium, the observed activation Gibbs free energy is

$$\Delta G_{stepwise}^\ddagger = \Delta G^\circ + \Delta G^\ddagger$$

The first value of the sum, ΔG° , could be computed by means of an analytical free energy calculation on the singlet and on the triplet optimized structures of $\text{MnOP}(\text{CH}_3\text{CN})^+$. Note that in order to take into account the solvation effects of acetonitrile, which is the solvent employed in the kinetics experiment, we replace the water axial ligand with the CH_3CN molecule. This acts as a first-sphere micro-solvation for the complex. The optimized structures of $\text{MnOP}(\text{CH}_3\text{CN})^+$ in the singlet and triplet state are depicted in Figure S9 in the SI. The ΔG° computed at 298.15 K amounts to 11.1 kcal/mol (we recall that $\Delta E = 10.2$ kcal/mol, see Table S1).

The second value of the sum, $\Delta G^\ddagger$, could be estimated as that arising from a bimolecular reaction occurring without a barrier, because the abstraction energy barrier is very small and hence its contribution to the free Gibbs energy is negligible. This kind of reaction should occur with a rate constant that is near the diffusion limit of 10^9 - $10^{10} \text{ M}^{-1} \text{ s}^{-1}$, and thus such step should have an activation free energy at 300 K of about 4 kcal/mol.^{20, 52} Hence, the theoretical value of $\Delta G_{stepwise}^\ddagger$ is about 15 kcal/mol.

In the kinetics studies performed by Newcomb and co-workers several different substrates for hydroxylation and epoxydation were employed and the measurements were all carried out at 295 K in acetonitrile.²⁰

The rate constant of Mn(V)OP detected for the oxidation of the ethylbenzene substrate, the closest compound to toluene employed by us, was found to be $k = (1.28 \pm 0.05) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ at 295 K. Using the Eyring equation, we obtain the value of $\Delta G_{exp}^\ddagger$.

$$\Delta G_{exp} = -R \cdot T \cdot \log\left(\frac{k \cdot h}{k_B \cdot T}\right) = 10.5 \text{ kcal/mol (10.4 kcal/mol at 295 K)}$$

The theoretical and the experimental values of $\Delta G^\ddagger$ are in reasonable agreement with a difference of 4.6 kcal/mol. The small energy difference between the two $\Delta G^\ddagger$ might arise mainly from the use of the BP86 functional that overestimates the singlet-triplet energy gap, and from the various assumptions we made in building the simplified model, first of all the absence of other species that are in the solution which have not been taken into account in our calculations (solvent molecules, basis, oxidizers, meso ligands,). In the context of this simplified stepwise reaction model, the three key aspects for the reactivity of MnOP species, namely spin-state crossing, equilibration of different oxidation states and pH-effects, can be easily rationalized in terms of the pre-equilibrium reaction (reac. 1). The value of ΔG° is evaluated as the singlet/triplet energy gap $\Delta E_{S/T}^\ddagger$ (spin-state crossing) whose value depends (among other factors) on pH-effects, as we have demonstrated in the axial ligand influence on reactivity analysis (see $\Delta E_{S/T}^\ddagger$ change along the X = H₂O, OH⁻ and O²⁻ series). In addition, the disproportionation equilibrium of Mn(IV) species is important in determining the concentrations of the active Mn(V) oxidant involved in reac.1. All of these three effects can thus control the reactivity through the pre-equilibrium step, particularly the Mn(III)/Mn(IV)/Mn(V) equilibria which may be responsible for the experimentally measured low product yields.

Conclusions

This work represents a theory/experiment reconciling study on the Mn-oxo porphyrins species reactivity for substrate hydroxylation. Kinetic and thermodynamic conclusions of MECP calculations on H-abstraction from toluene by MnOP(H₂O)⁺ have been deduced through deep investigations allowing to understand the reactivity. On the basis of MECP results, indicating a first crossover from a singlet spin state to a low-lying triplet spin state of the Mn-oxo porphyrin system, which represents the RDS with a thermally accessible barrier (6.5 kcal/mol), followed by a facile H-abstraction by the triplet complex from the toluene substrate ($\Delta E_{abstraction}^\ddagger = 0.5 \text{ kcal/mol}$), we investigated details of this reaction mechanism. The calculated high efficiency of the Mn-oxo porphyrins species for substrate oxidations even at thermal conditions is in sharp contrast with the experimental kinetic results by Newcomb and co-workers²⁰ where low yields of hydroxylation have been observed which might suggest that the RDS energy barrier is on the contrary very high. To solve this conundrum, we specifically focused on the following different issues. A first issue we addressed is the accuracy of the level of theory employed by us in DFT computations for a correct description of the Mn-oxo-

porphyrin system. We validated the singlet-triplet energy gap calculated for $\text{MnOP}(\text{H}_2\text{O})^+$ using the BP86 functional vs. accurate DMRG-CASPT2/CC results. The comparison shows that the BP86 functional overestimates the gap only slightly (about 2 kcal/mol), thus proving the reliability of our DFT results. A second issue concerns the influence of the axial ligand on $\text{MnOP}(\text{H}_2\text{O})^+$ reactivity. Different experimental reaction conditions have been modeled by considering additional trans axial ligand, different from water, which can be present in the reaction environment. We find that the singlet-triplet energy gap ranges between 6.0 and 10.0 kcal/mol for H_2O , OH^- , CH_3CN , Cl^- and none, suggesting that it is not much affected by such axial ligands, except in the case of very basic species (like O^{2-}) for which the singlet-triplet energy gap is largely increased (about 28 kcal/mol). The widening of the singlet-triplet energy gaps can be ascribed to the increasing trans influence, which mainly controls the reactivity. Yet another factor could finely tune the singlet-triplet energy gap, which is the porphyrin ruffling distortion. Finally, relying on our findings, a stepwise model for the H-abstraction process is proposed, where a first equilibrium between the singlet and triplet $\text{MnOP}(\text{CH}_3\text{CN})^+$ occurs and successively the triplet $\text{MnOP}(\text{CH}_3\text{CN})^+$ reacts with toluene under diffusion control (the reaction is virtually barrier-less). This reaction model allowed a final comparison with the high resolution experimental kinetic study by Newcomb and co-workers²⁰ where the active Mn(V)OPs are generated directly by laser flash photolysis. The agreement with experiment is surprisingly good: a theoretical free activation energy of 15.1 kcal/mol was calculated vs an experimental value of 10.5 kcal/mol. Furthermore, Newcomb and co-workers in their work suggested that the apparent low yields of hydroxylation are due to the fact that a small amount of Mn(V)OPs remains in the solution because of comproportionation and disproportionation equilibria giving Mn(IV)OPs and Mn(III)OPs, which have far less oxidation power. Our final result could be thought, within the restriction of the considered model, as a confirmation that such equilibria may be responsible for the low yields measured and, hence, could represent a starting point for future new investigations, both theoretical and experimental, aimed at improving the Mn-oxo porphyrin catalytic efficiency through variation of solution conditions.

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Conflict of interest

The authors declare no conflict of interest.

Keywords:

Mn-oxo porphyrins reactivity, hydroxylation reaction, density functional theory, minimum energy crossing point, DMRG-CASPT2/CC calculations

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Synopsis: Theoretical studies predict Mn(V)-oxo porphyrin species as very reactive intermediates in hydroxylation reactions with thermally accessible activation barriers represented by low spin/high spin crossover. On the other hand, experimental evidence for very low yields in such reactions has been provided. A stepwise model for the H-abstraction process is proposed which reconciles theory and experiment and allows to understand the reactivity of the Mn-oxo porphyrins.