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Probing the C-O bond-formation step in metalloporphyrin catalyzed C-H oxygenation reactions

Wei Liu^{†‡}, Mu-Jeng Cheng^{§||}, Robert J. Nielsen[§], William A. Goddard III^{*§}, and John T. Groves^{*†}

[†]Department of Chemistry, Princeton University, Princeton, New Jersey, 08544, United States

[§]Department of Chemistry, Materials and Process Simulation Center (MC 139-74), California Institute of Technology, Pasadena, CA 91125, USA

^{||}Department of Chemistry, National Cheng Kung University, Tainan 701, Taiwan

ABSTRACT: The oxygen rebound mechanism, proposed four decades ago, is invoked in a wide range of oxygen and hetero-atom transfer reactions. In this process, a high-valent metal-oxo species abstracts a hydrogen atom from the substrate to generate a carbon-centered radical, which immediately recombines with the hydroxometal intermediate with very fast rate constants that can be in the ns to ps regime. In addition to catalyzing C-O bond formation, we found that manganese porphyrins can also directly catalyze C-H halogenations and pseudohalogenations, including chlorination, bromination and fluorination as well as C-H azidation. For these cases, we showed that long-lived substrate radicals are involved, indicating that radical rebound may involve a barrier in some cases. In this study, we show that axial ligands significantly affect the oxygen rebound rate. Fluoride, hydroxide and oxo ligands all slow down the oxygen rebound rate by factors of 10-40 fold. The oxidation of norcaradiene by a manganese porphyrin coordinated with fluoride or hydroxide leads to the formation of significant amounts of radical rearranged products. *Cis*-decalin oxidation afforded both *cis*- and *trans*-decalol. Xanthene afforded dioxygen trapped products and the radical dimer product, bixanthene, under aerobic and anaerobic conditions, respectively. DFT calculations probing the rebound step show that the rebound barrier increases significantly (by 3.3, 5.4 and 6.0 kcal/mol, respectively) with fluoride, hydroxide and oxo as axial ligands.

KEYWORDS. Oxygen rebound, manganese porphyrin, iron porphyrin, hetero-rebound catalysis, DFT

Introduction

The heme-thiolate-containing monooxygenases, cytochrome P450, catalyze numerous highly selective transformations of aliphatic C-H bonds into C-OH bonds in biological systems under mild conditions.¹ A number of experiments, including positional scrambling in the allylic hydroxylation of olefins, loss of the stereochemistry in the hydroxylation center, as well as large kinetic isotope effects for hydroxylation, support the notion that this reaction proceeds via a stepwise hydrogen abstraction-radical recombination pathway.² In this oxygen rebound mechanism,³ the reactive high-valent oxoiron(IV) porphyrin cation radical, known as compound I,⁴ abstracts a hydrogen atom from the substrate to give a carbon radical intermediate, which then recombines with the iron-bound hydroxyl complex (formally Fe^{IV}-OH),^{4d,5} affording the alcohol products.

Inspired by the presence of an iron porphyrin core in the active site of cytochrome P450, our group and numerous others have developed metalloporphyrins and similar ligands containing various metals, such as Mn, Fe, Cr, Rh, Ru, for catalytic hydroxylation and epoxidation reactions in conjunction with terminal oxidants such as hydrogen peroxide, oxone, hypochlorite and PhIO.^{4e,6} Among these metalloporphyrins, manganese analogs have been studied extensively since they are known to be powerful mediators of oxygen transfer reactions. The catalytic oxidation reactions mediated by manganese porphyrins are also believed to proceed through the oxygen re-

bound mechanism, initiated via C-H abstraction by an oxoMn^V or *trans*-dioxoMn^V species.⁷ In the context that the C-H H-atom transfer step of these catalytic oxygenation reactions is rate-determining, many studies have explored the factors that affect the C-H abstraction ability of reactive oxo-metal species in order to mediate the reactivity.⁸

Scheme 1. Halogen rebound vs. traditional oxygen rebound in manganese porphyrin catalyzed C-H functionalization.

The second half of the mechanism, the C-O recombination step, is believed to go through a barrierless or low barrier substrate radical capture pathway. We have shown recently that in addition to catalyzing C-H oxygenation reactions, manganese porphyrins can also catalyze aliphatic C-H bond halogenations and pseudohalogenations, constructing C-Cl, C-Br, C-F and

even C-N bonds via direct C-H activation.⁹ Mechanistic studies of these halogenation reactions suggest that a common oxoMn^V species is involved as the key intermediate responsible for the C-H abstraction step. In contrast to the conventional C-H hydroxylation reactions, however, the substrate-derived radical does not recombine with the HO-Mn^{IV}(por) intermediate after the hydrogen abstraction step, but rather reacts with a high valent manganese hypohalite or manganese fluoride or azide intermediate (Scheme 1).¹⁰ Clearly, in these cases, the oxygen rebound event believed to occur immediately after C-H abstraction has taken a different path to transfer a different metal ligand. In addition, radical clock experiments have suggested the involvement of longer-lived radicals in these X-transfer reactions.

The novel halogenation reactivity of manganese porphyrins clearly indicates that *there is a previously unknown switch that can redirect the substrate-derived radicals from the fast hydroxyl rebound pathway to halogen rebound instead.* We anticipated that illuminating the nature of this switch could dramatically expand the reaction scope of metalloporphyrins C-H functionalization. Based on the observation that in our chlorination system, axial ligands of manganese porphyrins can change the selectivity of chlorination over hydroxylation, we proposed that axial ligands at the manganese center could affect the energetic barrier of oxygen rebound step.^{9a,11} More recently, Shaik, Nam, and Cho have provided DFT computational results supporting the notion that a non-rebound mechanism can be involved in some synthetic systems.^{12,6n,13}

We report herein a detailed experimental and theoretical study showing that axial ligands and *meso*-substituents of manganese porphyrin can have significant effects on the radical oxygen recombination step. This study provides the first experimental and theoretical insight into effects that can mediate oxygen rebound in the metalloporphyrin catalyzed oxidation reactions.

Results and Discussion

Oxidation of norcarane. We first studied the oxidation of a mechanistically diagnostic substrate, norcarane (**1**), catalyzed by a manganese porphyrin, Mn(TMP)OAc, in the presence of various amounts of tetrabutylammonium hydroxide (TBAH) or tetrabutylammonium fluoride (TBAF) (Table 1 and Figure S1). Acetonitrile was chosen as the solvent in order to prevent the formation of halogenated side products that are typically observed in halogenated solvents (e.g. CH₂Cl₂).¹⁴ In addition, acetate salts of manganese porphyrins were found to dissociate in acetonitrile and the axial ligand on the manganese center could be a weakly bound acetonitrile molecule. The reactions were run to approximately 5% conversion in order to prevent further oxidation of the alcohol products. Norcarane (**1**) has proven to be particularly useful to detect the radical intermediates in metalloporphyrin and metalloenzyme catalyzed hydroxylations.¹⁴⁻¹⁵ With the known rearrangement rate for 2-norcaranyl radical ($k = 2 \times 10^8 \text{ s}^{-1}$),^{15b} the radical lifetime could be determined from the ratio of rearranged product **1b** to unrearranged product **1a**. Oxidation of norcarane by *m*CPBA/Mn(TMP)OAc in the absence of TBAF or TBAH afforded 1-norcaranol (**1a**) as the major product with insignificant amounts of 3-hydroxymethyl cyclohexene (**1b**), implicating a fast radical recombination rate of $6 \times 10^9 \text{ s}^{-1}$ and thus a lifetime of 0.33 ns for the carbon radical intermediate. Such a recombination rate is close to that observed in early experiments with bicyclo[3.1.0]hexane as the diagnostic substrate in

cytochrome P450 system ($\sim 10^{10} \text{ s}^{-1}$).¹⁶ Interestingly, in the presence of TBAH or TBAF, the radical lifetime increased dramatically from 0.3 ns to 4 ns and $1 \times 10 \text{ ns}$, respectively. These radical lifetimes are similar to those observed in Mn-catalyzed chlorination and fluorination reactions.^{9a,9b} We attribute this increase of radical lifetime to an axial ligand effect on radical recombination. The coordination of hydroxide and fluoride anions to the manganese center was confirmed by the UV-Vis spectroscopy and control experiments showed that TBAF or TBAH alone do not react with any of the oxidation products.

Table 1. Oxidation of norcarane by Mn(TMP)OAc

Reaction conditions	Distribution %		
	1a	1b	others
Mn(TMP)OAc	76	5	19
Mn(TMP)OAc+5 eq TBAH	51	40	9
Mn(TMP)OAc+10 eq TBAF	25	67	8

Oxidation of *cis*-decalin. To further probe the effect of fluoride and hydroxide on the rebound step, we studied the loss of stereochemistry in the hydroxylation of *cis*-decalin (Table 2 and Figure S2-3). The degree of stereoretention was highly dependent on the manganese axial ligands. With no added axial ligand, Mn(TMP)OAc and Mn(TPFP)OAc hydroxylated *cis*-decalin with 90% and 95% stereoretention at the oxidized carbon center. Added TBAH and TBAF dramatically reduced the degree of retention, producing similar amounts of both stereoisomers. No oxygenated products were detected in the absence of manganese porphyrins. Since the *cis*-9-decalyl radical is known to invert to the trans conformation with a rate in excess of 10^8 s^{-1} ,¹⁷ similar to the rearrangement rate of norcaranyl radical, we conclude that the rate of carbon radical recombination in $[\text{R} \cdot \text{HO-Mn}^{\text{IV}}(\text{por})-\text{X}]$ is affected by the donor properties of the axial ligand X. By contrast, we have shown that Ru-porphyrins are efficient hydroxylation catalysts, which can catalyze the hydroxylation of *cis*-decalin affording *cis*-9-decalol and *cis*-decalin-9,10-diol exclusively.¹⁸ Similarly, Crabtree *et al.* showed that hydroxylation of *cis*-decalin with a Cp*Ir catalyst proceeded with almost complete retention of stereochemistry.¹⁹ Clearly, a long-lived *cis*-9-decalyl radical is not involved in either system and may reflect the low-spin preference for these second- and third-row metals. By contrast, the loss of stereochemistry in hydroxylation of *cis*-decalin is clearly shown in our study when the reaction is carried out in the presence of TBAH or TBAF (Table 2). The fact that the fraction of trans product increased with increasing amount of TBAF or TBAH further demonstrates the ability of fluoride and hydroxide ligands to increase radical lifetime.

Xanthene oxidation. Considering that the most well characterized oxoMn^V porphyrin complex is a *trans*-dioxoMn^V species,⁷ we investigated the effect of an oxo as a ligand on the oxygen rebound step. In order to compare hydroxo and fluoride with oxo, we chose xanthene (benzylic C-H BDE=75.5 kcal/mol²⁰) as the substrate, because *trans*-dioxoMn^V species

cannot cleave strong C-H bonds. When we added xanthene to a solution of $[\text{Mn}^{\text{V}}\text{TMP}(\text{O})_2]$ generated according to published procedure,⁷ we observed the formation of a $[\text{Mn}^{\text{IV}}\text{TMP}(\text{O})(\text{OH})]$ complex (Figure S6), consistent with an earlier report²¹ and clearly showing that oxygen rebound is *not* involved in the reaction.

Table 2. Oxidation of *cis*-decalin by manganese porphyrins.^a

Entry	porphyrins	additive	equiv additive	2a/2b ratio
1	Mn(TPFPP)OAc	-	-	>20
2	Mn(TPFPP)OAc	TBAH	2	>20
3	Mn(TPFPP)OAc	TBAH	5	11.1
4	Mn(TPFPP)OAc	TBAH	10	0.7
5	Mn(TMP)OAc	-	-	10
6	Mn(TMP)OAc	TBAF	5	1.1
7	Mn(TMP)OAc	TBAF	10	0.8

^a Reactions were run under nitrogen in acetonitrile.

Scheme 2. Xanthene oxidation under $^{18}\text{O}_2$ atmosphere

When the catalytic xanthene oxidations were carried out under an $^{18}\text{O}_2$ (97%) atmosphere, we found that the degree of ^{18}O incorporation into the major product, xanthone, significantly increased when TBAH or TBAF is present (Scheme 2 and Figure S7). Less than 5% ^{18}O was incorporated in xanthone in the absence of hydroxide or fluoride, consistent with an oxygen rebound pathway involving xanthyl radical. In the presence of 20 equiv. of TBAH (the *trans*-dioxo species is formed under these conditions) or 30 equiv. TBAF, we observed 48% and 84% of ^{18}O , respectively, into the xanthone carbonyl. The lower ^{18}O incorporation in the TBAH case was due to the exchange of xanthone- ^{18}O with ^{16}O -hydroxide in TBAH. Apparently, in these cases, the xanthyl radical, generated via C-H abstraction by the oxo Mn^{V} species, is trapped by $^{18}\text{O}_2$ rather than the HO- Mn^{IV} intermediate. These isotope-labeling experiments are consistent with the hypothesis that the substrate radical cage escape pathway competes with the oxygen rebound pathway when hydroxo, fluoro or oxo ligands occupy the trans position on the metal center (Scheme 3).

When xanthene oxidations are carried out under a nitrogen atmosphere (Figure S4-S5), we found that bixanthene (**3c**) was

formed at the expense of xanthone (**3b**) and xanthylol (**3a**), indicating that the radical intermediate is in sufficient concentration to dimerize. The formation of bixanthene has also been observed by Mayer in the $\text{Mn}(\text{hfacac})_3$ oxidation system.²² Importantly, the distribution of **3c** in the product mixture increases with increasing amounts of TBAH and TBAF (Table S1), suggesting that the lifetime of 9-xanthyl radical increases when fluoride, hydroxide and oxo are the axial ligands. Furthermore, we interpret the distribution of bixanthene in the product mixture as indicating the fraction of radicals that escape from the radical cage. The plot of percentage of escaped radical as a function of TBAF concentration reveals clear saturation behavior (Figure 1), suggesting a pre-equilibrium between $\text{Mn}^{\text{V}}(\text{TMP})(\text{O})$ and $(\text{F})\text{Mn}^{\text{V}}(\text{TMP})(\text{O})$, with a $K_d = 24 \pm 2$ mM. Goldberg and de Visser also observed a similar pre-equilibrium in the manganese corrolazine system.²³ On the basis of aerobic and anaerobic oxidation of xanthene, we conclude that hydroxo, fluoride, and oxo ligands are all able to decelerate the oxygen rebound rate so that the radicals generated via C-H abstraction under these conditions have much longer lifetimes than those in traditional oxygenation reactions. This deceleration of the radical recombination rate explains the xanthyl radical trapping by oxygen and the one-electron reduction of $\text{Mn}(\text{V})$ to $\text{Mn}(\text{IV})$ that has been reported for a similar system.²¹

Scheme 3. Two different pathways in xanthene oxidation by manganese porphyrin.

Figure 1. Effect of fluoride concentration on escaped radical. The plot of percentage of escaped radical against TBAF concentration affords a $K_d = 24 \pm 2$ mM for the equilibrium between $\text{Mn}^{\text{V}}(\text{TMP})(\text{O})$ and $(\text{F})\text{Mn}^{\text{V}}(\text{TMP})(\text{O})$. The concentration of total manganese porphyrin is ~ 5 mM.

Comparison between manganese and iron porphyrins. Encouraged by the ligand effect on Mn-catalyzed oxidation reactions, we further expanded our studies to iron analogs, considering that nature has evolved iron-heme containing enzymes for a wide range of oxidation reactions. In order to study the rebound step in Fe-catalyzed C-O bond formation, we prepared the optically pure *S*-(1-deuterioethyl)-benzene (**4**) as a hypersensitive substrate. This chiral probe has been shown to be useful for the examination of both cytochrome P450 and model iron porphyrin oxygenations.^{2d,24} Generally, hydroxylation of **4** could potentially provide a mixture of deuterated and non-deuterated *R* and *S* phenylethanol (**4a-4d**). Determination of the composition of the four components according to the published procedure^{2d} could allow us to describe the degree of stereo-specificity, which can be quantitated by the extent of net retention (Scheme 4 and Scheme S1). Based on the known time constants for rotation of medium size radicals in fluid solvents (5-20 ps),²⁵ we expect that **4** can probe very fast radical rebound events with rate constants in the range of 10⁹-10¹¹ s⁻¹.

Scheme 4. Oxidation of optically pure 1-d-ethylbenzene.

Samples of optically pure **4** were prepared by the method of Mosher.²⁶ We first studied the oxidation of **4** with manganese and iron porphyrins bearing four different *meso*-substituents, TMP (tetramesityl), TDCIP (2,6-dichlorophenyl), TDFPP (2,6-difluorophenyl) and TPFPP (pentafluorophenyl) (Table 3, Entry 1-2). Two observations are immediately apparent from these studies: (1) the net retention increased with increasing electron withdrawal of the *meso*-substituents on porphyrin rings in both the manganese and iron cases, and (2) Fe-catalyzed hydroxylation reactions always afforded much higher degrees of stereoretention than manganese analogs with the same *meso*-substituents. We observed a similar effect when achiral ethyl benzene was hydroxylated with chiral iron and manganese porphyrins.²⁷ Thus, the intermediate substrate radicals are generally longer-lived with manganese porphyrin catalysts.

Table 3. Effect of *meso*-substituents, axial ligands on the net retention.^a

Entry	Metal/Ligand	Net Retention (%)
1	Mn/Cl	8
2	Fe/Cl	80
3	Fe/F	62

^a Determinations of at least three oxidations were reproducible to $\pm 1\%$. Reactions were run to approximately 10% conversion.

We also investigated the effect of fluoride ligation on the Fe-catalyzed C-O bond formation step. Different iron porphyrins bearing fluoride axial ligands were prepared by treating the corresponding chloride salts with silver fluoride. As illustrated in entry 3, coordinating fluoride with iron porphyrins, drastically decreased the degree of net retention ($\sim 20\%$), similar to observations for the manganese analogs. We assign the reactive intermediates in these reactions as oxo iron(IV) porphyrin cation radicals with fluoride as axial ligand based on the following considerations: (1) UV-Vis spectra showed that fluoride anion does not dissociate from the iron center after the reactions are completed and (2) it has been shown that treatment of iron(III) porphyrins with oxygen donors, such as *m*CPBA or ozone, results in formation of iron(IV) porphyrin cation radicals without losing their anionic ligands.^{8a}

DFT calculations on the oxygen recombination step. To gain more insight into this unprecedented ligand effect on the oxygen rebound step, we performed DFT calculations at the B3LYP level with Poisson-Boltzmann continuum solvation to obtain free energies at 298 K on the rebound of methyl radical to a (X)Mn^{IV}(THP)(OH) (THP = tetrahydroporphyrin) species bearing various axial ligands X (Scheme 5A) (full details in the Supporting Information).

We found that the (X)Mn^{IV}(THP)(OH) fragment with X = H₂O, CH₃CN, F⁻, or OH⁻ has a spin quartet ground state (S=3/2) with three singly occupied orbitals d_{xy} , d_{xz} , and π^*_{yz} , whereas X = O²⁻ has a spin doublet state (S=1/2) with a doubly occupied d_{xy} , a singly occupied d_{xz} , and an empty π^*_{yz} orbital. All the Mn^{IV}/methyl caged complexes are in a low-spin ground state (5-L) except CH₃CN, in which the spins of (X)Mn^{IV}(THP)(OH) and the methyl radical are aligned. Rebound reactions proceed through the transition states **5,6-TS**, leading to products **6**. In **5,6-TS**, the unpaired electron of the methyl radical interacts with the $\sigma^*_{z^2}$ of (X)Mn^{IV}(THP)(OH) (Scheme 5B), resulting in a nearly linear ($\sim 170^\circ$) Mn-O-C geometry.²⁸

Scheme 5. Schematic depiction of (A) methyl rebound reaction and (B) orbital interactions in rebound transition states (1,2-TS).

What is most striking from the DFT calculations is the increase of the oxygen rebound barrier that is found for coordination of axial ligands having different electron-donating abilities to the HO-Mn^{IV}(THP) species. The rebound barrier increases from 2.1 and 2.4 kcal/mol for X = H₂O and CH₃CN, respectively, to 5.4, 7.5, and 8.1 kcal/mol upon coordination of F⁻, OH⁻ and O₂⁻, respectively (Figure 2). This increase in the rebound barrier is in excellent agreement with the experimental results that F⁻, OH⁻ and O₂⁻ dramatically decelerate the rebound rate, leading to formation of long-lived radicals, which undergo rearrangement, isomerization, or dimerization. In addition, comparison of the rebound barrier between [R•HO-Mn^{IV}(TPP)-OH] and [R•HO-Mn^{IV}(TPFPP)-OH] shows that the barrier of the latter case is lower by 1.9 kcal/mol, consistent with the experimental results that high net retention numbers were observed for porphyrins bearing electron-withdrawing *meso*-substituents. A likely explanation for this effect is a higher redox potential for the HO-Mn^{IV} intermediate, leading to faster electron transfer from the substrate radical to the manganese(IV) center.

We rationalize the variation in rebound barriers as due to the difference in electron-donating ability of the axial ligands. As the axial ligand or *meso*-substituent become more donating, the $\sigma^*_{z^2}$ orbital is destabilized. Since the oxygen rebound step reduces Mn^{IV} to Mn^{III}, the destabilization of the frontier orbital that is going to host the one substrate-derived electron will lead to an increase in rebound barriers. This hypothesis is supported by the orbital energy of $\sigma^*_{z^2}$, which increases as the axial ligands vary from H₂O, CH₃CN, F⁻, to HO⁻ (Figure 3). Due to the difference in the character for the ground state of X = O₂⁻, where both π^*_{yz} and $\sigma^*_{z^2}$ are unoccupied, we cannot compare its orbital energies with the others. However, based on its longer Mn-OH bond length (1.89 Å) compared to the others (1.75, 1.76, 1.80, and 1.82 Å for X = H₂O, CH₃CN, F⁻, and OH⁻, respectively), we estimate that the orbital energy of $\sigma^*_{z^2}$ for X = O₂⁻ is more destabilized than the others, leading to the higher rebound barrier.

Another way to access the electron-donating ability of the axial ligands is to calculate one-electron reduction potentials (E_h 's) for Mn(THP) with X = CH₃CN, H₂O, F⁻, and OH⁻. Using 4.44 eV as the thermodynamic work function of the standard hydrogen electrode (SHE), we calculated the E_h 's to be 0.88, 0.59, -0.14, and -0.31 V vs SHE, respectively. Thus the E_h 's correlate strongly with the barriers for the methyl rebound step.

Figure 2. Rebound potential energy surfaces for methyl radical interacting with Mn^{IV}-OH (electronic plus solvation energies) with various axial ligands in CH₂Cl₂ solvent. All energies are in kcal/mol.

Interestingly, we find that the rebound barrier can be tuned by up to nearly 3 kcal/mol through the solvent dielectric constant (ϵ_r): rebound barriers increase as ϵ_r increases (Table S2). For example, the barrier for X = F⁻ with THP is only 3.1 kcal/mol in vacuum, while it increases gradually to 4.2, 5.4, 5.7, and 5.8 kcal/mol as ϵ_r increases to 2.0, 8.93, 20.0, and 40.0. This is because the negatively charged hydroxo oxygen in **1** is exposed to solvent stabilizing it by interactions with higher dielectric constant solvents (Figure 4). In the transition state, the methyl fragment shields the interaction of the hydroxo ligand and solvent, leading to less solvation stabilization and therefore a larger barrier. This shielding effect is larger in the top-attack transition state than in side-on attack. For $\epsilon_r \leq 2$, we predict that high-spin, top-attack is preferred, but for larger dielectric constants, side attack becomes more favorable.

This suggests that the selectivity between radical recombination and cage escape following alkane hydrogen abstraction by the oxoMn^V complex can be influenced by solvents. We predict the rebound pathway to be encouraged in low dielectric constant solvents, leading to more hydroxylation products. On the other hand, the rebound pathway is suppressed in high dielectric constant solvents, increasing the escape of alkyl radicals that can or form dimers or lead to alkyl chlorides by reacting with other substrates in the system such as hypochlorite adducts. It should be noted that in this work we used implicit solvation model, which only considers the electrostatic interaction between substrate and solvent, and ignores the rigidity of the solvent. The latter may play some roles in the rebound process.

Figure 3. The influence of axial ligands on the Mn^{IV} orbital energies of the singly occupied π^*_{yz} and unoccupied $\sigma^*_{z^2}$. The π^*_{yz} orbital energy of $\text{X} = \text{H}_2\text{O}$ is taken as the reference point. The rebound barriers are given in the table below the figure.

Indeed, Arunkumar et al. found that in basic aqueous solution ($\text{pH} = 10.5$) the oxo Mn^{IV} porphyrin complex is converted to hydroxo Mn^{IV} after activating C-H bonds of alkylaromatic substrates. This reaction does not proceed to the Mn^{III} porphyrin and alcohol. This suggests that there is a significant rebound barrier driving the reaction to 100% radical escape. This high radical escape ratio is due both to use of a basic solution and to the use of water as the solvent. Water has a high dielectric constant ($\epsilon_r = 80.37$), which our theoretical studies find to increase the oxygen-rebound barrier even higher.

Figure 4. Electrostatic potential (calculated in vacuum) projected on van der Waals surfaces of **1L**, **1,2-TS-H**, and **1,2-TS-L** of $\text{X} = \text{OH}^-$ with **THP**. A rainbow color ramp is utilized with the red color representing the most negative and the purple representing the most positive electrostatic potential.

Conclusions

We have shown here that axial ligands as well as *meso*-substituents play an important role in the C-O bond forming oxygen rebound step. Fluoride, hydroxide, or oxo ligands can dramatically decelerate the rate of substrate radical recombination in Mn-porphyrin catalyzed C-O bond forming reactions, giving the intermediate time to rearrange or completely escape the catalyst-substrate solvent cage and dimerize. Manganese porphyrins bearing electron-withdrawing *meso*-substituents, such as pentafluorophenyl porphyrin, results in increased radical recombination rates on the rebound step. Faster oxygen rebound rates are observed for the iron porphyrins than for the manganese analogs.

Clearly, our results indicate that appropriate choices of metalloporphyrin and coordinating ligands are crucial to achieving stereospecific reactivity. Fluoride and hydroxide should be avoided when stereo-retentive C-H oxygenation is desired. One reason why nature has chosen cysteine thiolate-ligated Fe-heme enzymes is probably to avoid the generation of long-lived radicals. On the other hand, addition of appropriate ligands that can slow down the oxygen rebound rate is necessary

for achieving novel C-H halogenation reactivity. Stronger donor ligands such as fluoride and hydroxide create a significant kinetic barrier for the oxygen rebound step, leading to the recombination of radicals to Mn-heteroatom species (Hetero-Rebound). New catalysts and methodologies based on this Hetero-Rebound Catalysis (HRC) strategy are currently being explored in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental and computational details, supplementary figures and tables. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

* jtgroves@princeton.edu, wag@wag.caltech.edu

Present Addresses

[†]Department of Chemistry, University of California Berkeley, Berkeley, CA 94720

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