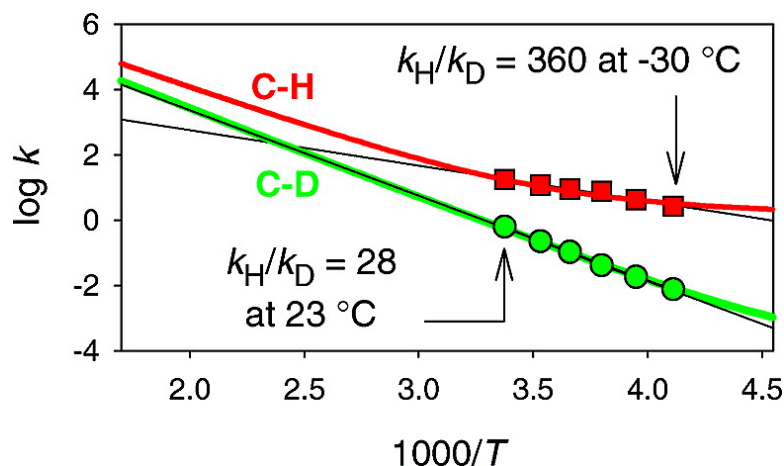## Communication

Tunneling in C#H Oxidation Reactions by an Oxoiron(IV) Porphyrin Radical Cation: Direct Measurements of Very Large H/D Kinetic Isotope Effects

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Tunneling in C—H Oxidation Reactions by an Oxoiron(IV) Porphyrin Radical Cation: Direct Measurements of Very Large H/D Kinetic Isotope Effects

Zhengzheng Pan, John H. Horner, and Martin Newcomb*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607

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Enzyme-catalyzed C—H oxidation reactions have been a subject of considerable research interest for decades due to the high energy demand of the reactions. Models of iron-containing enzymes include iron—porphyrin complexes that are based on heme enzymes such as the cytochrome P450 enzymes. These models function as oxidation catalysts when they are activated by sacrificial oxidants that give high-valent iron—oxo complexes.[1] For oxidations of C—H bonds, the transient catalyst oxidants usually have an iron atom in the formal +5 oxidation state. The observable highly oxidized models for the heme-containing enzymes are oxoiron(IV) porphyrin radical cations, examples of which were characterized as early as the 1980s.[2]

Among the more intriguing features of enzyme-catalyzed C—H oxidations are very large H/D kinetic isotope effects (KIEs) ranging up to 100 found in, for example, the hydrogen-atom abstractions of lipoxygenase[3] and insertions of oxygen into a C—H bond of methane by methane monooxygenase enzymes.[4] Such large KIEs are ascribed to hydrogen atom tunneling reactions that can be optimized in the enzyme by controlling residue positions in the active site and can include vibrational or gating processes.[5] We report here that very large H/D KIEs due to tunneling can be observed in C—H hydroxylation reactions effected by an ox-oiron(IV) porphyrin radical cation under single turnover conditions.[6–8] Quantifications of the tunneling reactions are expected to have ramifications for understanding enzyme-catalyzed oxidation reactions and to serve as benchmarks for computational studies of C—H oxidation reactions.

5,10,15,20-Tetramesitylporphyriniron(III) chloride and perchlorate complexes (TMP)Fe^{III}(X) were oxidized with m-chloroperoxybenzoic acid (mCPBA) to give the known oxoiron(IV) porphyrin radical cations (TMP)$^{+•}$Fe^{IV}(O)(Cl) and (TMP)$^{+•}$Fe^{IV}(O)(ClO$_4$).[2,9,10] The iron—oxo complexes reacted smoothly in pseudo-first-order processes with large excesses of substrates (benzyl alcohol or ethylbenzene) in acetonitrile in reactions with clear isosbestic points (Figure 1). The substrates are oxidized at the benzylic positions to give, respectively, benzaldeyde and 1-phenylethanol (see Supporting Information).[9]

Variable temperature kinetic studies were conducted over the temperature range of −30 to 23 °C. Rate constants were measured for a series of pseudo-first-order reactions at a given temperature, and the second-order rate constants were determined from eq 1, where k_{obs} is the observed pseudo-first-order rate constant, k_0 is a background rate constant (ca. 0 in these studies), k_{ox} is the second-order rate constant, and [sub] is the substrate concentration. The results are in Table 1.

$$k_{obs} = k_0 + k_{ox}[sub] \tag{1}$$

For oxidation of benzyl alcohol, a large KIE value was observed at ambient temperature, and tremendous KIE values were found at lower temperatures. The series of reactions with four isotopomeric benzyl alcohols at 23 °C confirmed that the KIE effect was from
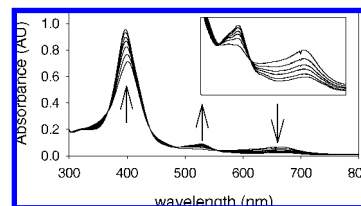

Figure 1. Time-resolved UV—vis spectrum for reaction of **2** (X = ClO$_4$) with 5.0 mM benzyl alcohol in CH$_3$CN at 23 °C; the time period is 5–50 s after mixing. The inset is an expansion of the region $\lambda = 450–750$ nm.

Table 1. Second-Order Rate Constants for Reactions of (TMP)$^{+•}$Fe^{IV}(O)(ClO$_4^−$) in CH$_3$CN

substrate[a]	temp[b]	k_{obs}(H)[c,d]	k_{obs}(D)[c,e]	KIE[f]
BA	23	17.5 ± 1.4	0.62 ± 0.02	28 ± 2
	23	16.7 ± 1.6[g]	0.64 ± 0.04[h]	
	10	11.8 ± 0.4	0.22 ± 0.02	54 ± 5
	0	8.8 ± 0.2	0.104 ± 0.006	85 ± 5
	−10	7.56 ± 0.15	0.040 ± 0.002	190 ± 10
	−20	4.20 ± 0.08	0.0179 ± 0.0009	235 ± 12
	−30	2.67 ± 0.06	0.0074 ± 0.0003	360 ± 20
EB	22[i]	1.64 ± 0.07	0.030 ± 0.001	55 ± 3
EB[j]	22[i]	4.7 ± 0.2	0.100 ± 0.008	47 ± 4

[a] BA = benzyl alcohol; EB = ethylbenzene. [b] Temperature in °C ± 0.1. [c] Second-order rate constants in units of M$^{−1}$ s$^{−1}$ with errors at 1σ. [d] Rate constant for the undeuterated isotopomer. [e] Rate constant for benzyl alcohol-d_7 or ethylbenzene-d_{10}. [f] Observed kinetic isotope effect with error at 1σ. [g] The substrate was C$_6$D$_5$CH$_2$OH. [h] The substrate was C$_6$H$_5$CD$_2$OH. [i] ±0.5 °C. [j] (TMP)$^{+•}$Fe^{IV}(O)(Cl) was the oxidant; an increased reactivity of the complex with the "stronger" chloride ligand is known,[9b] and a limit of KIE >20 for reaction of this oxidant with benzyl alcohol at low temperature was reported.[9a]

oxidation of the benzylic position. Specifically, C$_6$D$_5$CH$_2$OH reacted with the same rate constant as C$_6$H$_5$CH$_2$OH, and C$_6$H$_5$CD$_2$OH reacted with the same rate constant as C$_6$D$_5$CD$_2$OH. Studies with ethylbenzene demonstrated that the large KIE phenomenon was not specific to the substrate benzyl alcohol nor to the perchlorate counterion in the iron—oxo complex; it was a function of the porphyrin, however (see below).

The temperature-dependent data for benzyl alcohol-d_0 and -d_7 require that tunneling is the major process in the oxidation reaction of the undeuterated isotopomer. Because we studied single turnover reactions, the KIEs must be ascribed to the single elementary reaction. For benzyl alcohol-d_7, the reaction appears to have conventional second-order entropic and enthalpic terms of log A = 8.6 and E_a = 12.0 kcal/mol. The reaction of undeuterated benzyl alcohol is the unusual case with an apparent Arrhenius preexponential term (log A = 4.9) that is not possible when compared to the value for the perdeuterated isotopomer as well as an impossibly small activation energy (E_a = 5.0 kcal/mol). Specifically, the E_a term for the "D" reaction is 7.0 kcal/mol greater than that for the
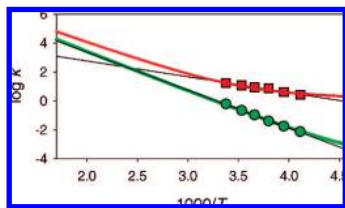
Figure 2. Analysis of the kinetic data for oxidations of benzyl alcohol by $(TMP)^{+\bullet}Fe^{IV}(O)(ClO_4)$. The symbols are observed rate constants for reactions of benzyl alcohol-d_0 (red) and benzyl alcohol-d_7 (green). The black lines are the apparent Arrhenius functions. The colored lines are predicted rate constants using the parabolic energy barrier model of Bell (ref 12a) with the parameters listed in the text.

"H" reaction, but the classical H/D KIE model *requires tunneling contributions* when $\Delta E_a > 1.2$ kcal/mol.[11]

The benzyl alcohol data can be analyzed by various tunneling models.[12] The parabolic energy barrier model described by Bell[12a] is shown in Figure 2. An excellent fit was obtained for a chemical reaction with log $A = 9.0$, $E_a(H) = 12.1$ kcal/mol, and $E_a(D) = 13.3$ kcal/mol when combined with a tunneling reaction with a barrier half-width (a) of 0.43 Å. Tunneling is by far the major process for oxidation of $C_6H_5CH_2OH$; at room temperature, the tunneling reaction represents 93% of the total reaction. In the terminology of Bell,[12] $Q = 13$ at room temperature.

A large tunneling component for the hydroxylation reactions of the benzylic positions we found likely also explains the origin of results reported for oxidations of cyclohexene by $(TMP)^{+\bullet}$-$Fe^{IV}(O)(Cl)$.[13] Widely different Arrhenius functions were found for the competing epoxidation and hydroxylation reactions of cyclohexene,[13] where the allylic hydroxylation reaction had a remarkably small activation energy, apparently because hydroxylation involved a significant tunneling component. The authors noted that computational results for oxoiron(IV) porphyrin radical cations are not reliable because they do not account for the differences between entropic versus enthalpic control in the competing reactions.[13] That conclusion may be qualified because the tunneling component expressed in the hydroxylation reaction by the TMP complex is not expressed to the same extent with other porphyrins.

The effect of porphyrin identity on the tunneling reaction can be evaluated in single turnover (absolute kinetics) or catalytic (competition kinetics) reactions. In single turnover studies, the KIEs for $(Por)^{+\bullet}Fe^{IV}(O)(X)$ oxidations change dramatically with the porphyrin macrocyclic ligand.[10] The KIE for oxidations of ethylbenzene-d_0 and -d_{10} by $(TPFPP)^{+\bullet}Fe^{IV}(O)(ClO_4)$ was only 4.4,[9] much smaller than the value of 55 found for the TMP species. Similarly, the KIEs found in oxidations of benzyl alcohol-d_0 and -d_7 by three oxoiron(IV) porphyrins containing electron-withdrawing aryl groups were small (4.5–5.7).[14]

The same trends are found in catalytic processes. For a series of catalytic oxidations of benzyl alcohol-d_0 and -d_7 mixtures in CH_3CN at 0 °C with mCPBA as the sacrificial oxidant, we found $k_H/k_D = 30 \pm 3$ for $(TMP)Fe^{III}(ClO_4)$, $k_H/k_D = 11 \pm 2$ for $(TPP)Fe^{III}Cl$, and $k_H/k_D = 3.9 \pm 0.8$ for $(TPFPP)Fe^{III}Cl$. Similarly, the KIEs in catalytic oxidations of cyclohexane-d_0 and -d_{12} by $(TMP)Fe^{III}(Cl)$ are large,[7,15] whereas those for the cyclohexane oxidations catalyzed by halogen-containing aryl-substituted porphyrin−iron(III) complexes are small.[16] The reduction of the apparent KIEs in the catalytic processes might result because a nonisotopically sensitive step is partially rate-determining in a composite reaction or because a more reactive oxidant[18] is formed in the catalytic cycle.

In either single turnover or catalytic processes, the qualitative trend is that the KIE values decrease with increasing electron withdrawal by the porphyrin. The relationship appears to be complex and not due solely to an increased chemical reactivity for the electron-withdrawing porphyrins.[17] For example, the rate constants for oxidations of benzyl alcohol are similar for $(TPFPP)Fe^{IV}(O)(X)$ (normal KIEs) and $(TMP)^{+\bullet}Fe^{IV}(O)(X)$ (large KIEs).[9,19] These results suggest that computational quantification of the phenomenon will be difficult.

In summary, hydroxylation reactions of benzylic C−H positions by $(TMP)^{+\bullet}Fe^{IV}(O)(X)$ occur mainly by tunneling at room temperature, resulting in large H/D KIEs similar to those found with some non-heme iron enzyme[3,4] and oxoiron(IV) reactions.[8] Given the large number of heme-containing enzymes, such tunneling reactions might be important in enzyme-catalyzed hydroxylations where barrier widths for tunneling can be modulated by the enzyme.[5] The tunneling results provided in this work should serve as a benchmark for computational studies of oxidations by heme-containing enzymes and their models.

Supporting Information Available: Experimental description of kinetic studies and detailed results. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Abbreviations: TMP = 5,10,15,20-tetramesitylporphyrin; TPFPP = 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin; TPP = 5,10,15,20-tetraphenylporphyrin; Por = porphyrin.
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