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Isotope Effects

A Two-State Reactivity Model Explains Unusual Kinetic Isotope Effect Patterns in C–H Bond Cleavage by Nonheme Oxoiron(IV) Complexes**

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The surging field of nonheme iron chemistry has led to the identification of a variety of iron(IV) oxo intermediates, which perform oxidative processes such as hydrogen-atom abstraction (H-abstraction) and oxo-transfer reactions with a variety of molecules.[1–3] The advent of both enzymatic and synthetic examples has revealed in turn some puzzles of fundamental importance in mechanistic bioinorganic chemistry. Thus, whereas the known enzymatic species, for example, in taurine/α-ketoglutarate dioxygenase (TauD),[4] have been shown by Mössbauer analyses to possess a ground state with a quintet spin (Q) quantum number ($S=2$), all except one of the synthetic iron oxo species have been shown by experimental means to possess triplet (T) ground states ($S=1$) and low-lying quintet states.[2,3] Nevertheless, some of the reactivity patterns of the enzymatic and synthetic reagents are still similar. For example, use of deuterated taurine in reactions with TauD has revealed a kinetic isotope effect (KIE) of approximately 37 for the decay of the iron oxo species.[4,5] The synthetic compounds $[\mathrm{Fe^{IV}(O)(N4Py)}]^{2+}$ (**1**, N4Py = *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine) and $[\mathrm{Fe^{IV}(O)(BnTPEN)}]^{2+}$(**2**, BnTPEN = *N*-benzyl-*N*,*N*′,*N*′-tris(2-pyridylmethyl)-1,2-diaminoethane),[6,7] despite possessing triplet ground states, also exhibit large KIE values (greater than 30) for H-abstraction from ethylbenzene versus [D$_{10}$]ethylbenzene.[6] A primary isotope effect supports a rate-determining C–H bond cleavage. Furthermore, the observation of such large KIEs for both the enzymatic and model system reactions suggests that the reactivity of **1** and **2** is analogous to the enzyme, namely, that the excited quintet states of **1** and **2** must somehow be involved in C–H activation.[2,3] If this is indeed the case, the reactions of the synthetic reagents should involve two-state reactivity (TSR),[8] in which both the triplet and quintet states contribute to the overall bond activation. Subsequent calculations[9] indeed showed the probable involvement of TSR, since the excited quintet state lies close to the triplet ground state and the triplet surface eventually crosses over to the quintet surface as the reaction progressed.

The insight provided by the TSR model was utilized recently to rationalize the counterintuitive results observed when the series of $[\mathrm{Fe^{IV}(O)TMC(X)}]^{z+}$ reagents (TMC = tetra(*N*-methyl)cyclam, X = MeCN, trifluoroacetate (TF), N_3, or thiolate (SR)) led to opposing reactivity trends in H-atom abstraction versus oxo-transfer reactions.[10] A systematic study of the series demonstrated that the oxo-transfer capability of $[\mathrm{Fe^{IV}(O)TMC(X)}]^{n+}$ towards $\mathrm{PPh_3}$ increased in the order $\mathrm{X = SR < N_3 < TF < MeCN}$, but the reactivity in H-abstraction from 9,10-dihydroanthracene (DHA) decreased in the order $\mathrm{L = SR > N_3 > TF > MeCN}$, which is in the opposite direction. Thus, the $[\mathrm{Fe^{IV}(O)TMC(X)}]^{n+}$ oxidant exhibited a dichotomic reactivity pattern: in the oxo-transfer series it behaved as an electrophile whereby electron-releasing anionic ligands X diminished the oxidative reactivity, whereas in the C–H activation series the best H-abstractor was the poorest oxidant with X = SR. The TSR concepts showed that the involvement of the quintet state in the reaction is the origin of these unusual reactivity patterns. Further validation of the TSR model was obtained from a more recent study on the corresponding $[\mathrm{Ru^{IV}(O)TMC(X)}]^{n+}$ oxidants, in which the quintet state is too high to be able to participate in the reaction;[11] this study revealed that the two reaction series exhibit precisely the same trends, which is indicative of the sole involvement of the triplet state.

We wished to investigate if it was possible to more directly interrogate the TSR concept by experimental means. A set of criteria has been suggested that could be used to probe the feasibility of a TSR system.[9a,10b] It was hypothesized that the crossover from triplet to quintet states provides a tunneling-like pathway that may be probed by an investigation of KIEs. Thus, the TSR model assumes that triplet processes will exhibit nearly classical values for k_H/k_D. For the quintet process, or in a process where spin crossover from triplet to quintet occurs, values for k_H/k_D that are typical of a tunneling mechanism were predicted. However, the critical prediction was that the KIE should vary with the strength of the C–H bond between the classical (less than ca. 7) and nonclassical (much greater than 7) limits. Herein, we report the test of this

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working hypothesis and present a study of hydrocarbon oxidation by **1** and **2**. Our results serve as a demonstration of the complementary roles that experiment and theory can play in a mechanistic investigation.

Previous studies on the reactions of **1** and **2** with ethylbenzene (PhEt) and [D$_{10}$]PhEt showed high, nonclassical k_H/k_D values of 30 and 50, respectively, for reactions performed at 25 °C.[6] KIEs of this magnitude are often associated with a mechanism that involves hydrogen-atom tunneling. However, there are more stringent criteria to invoke a tunneling model, which may be established from an evaluation of the temperature dependence of the reaction rates by analysis of their Arrhenius plots. Features representative of a reaction that involves hydrogen-atom tunneling include a difference in energies of activation ($E_{aH}-E_{aD}$) for the systems greater than the zero-point energy differences (ΔZPE) of the reactant C–H and C–D bonds and a ratio of the Arrhenius prefactors that yields A_H/A_D to be less than 0.7.[12,13] Figure 1 shows the temperature dependences of the rates of the reaction of **2** with PhEt from −40 to 40 °C and the reaction of **2** with [D$_{10}$]PhEt from 10 to 50 °C. From these plots, it can be deduced that the KIE increases significantly from a value of 40 at 40 °C to a value of 400 at −40 °C. E_a values of 7.8 (3) and 12.0 (1) kcal mol^{-1} can be obtained from the temperature-dependence plots for the oxidations of PhEt and [D$_{10}$]PhEt by **2**, which correspond to a ΔE_a of 4.2 kcal mol^{-1}. The ΔZPE for the benzylic hydrogen and deuterium atoms of PhEt can be obtained from vibrational data, which shows a downshift of approximately 800 cm^{-1} upon deuterium substitution; this shift corresponds to an energy difference of 2 kcal mol^{-1}. Therefore, ΔE_a is greater than ΔZPE. Additionally, the Arrhenius plots give an A_H/A_D ratio of 0.03, a value much lower than 0.7 and consistent with enzymatic systems that are shown to involve hydrogen-atom tunneling.[13] Thus, the reaction of **2** with PhEt exhibits all the necessary and sufficient characteristics expected for a reaction involving H-atom tunneling. The values obtained here for **2** are comparable to those recently reported by Newcomb and co-workers on the temperature dependence of the KIEs for the oxidation of benzyl alcohol by [Fe^{IV}(O)(TMP$^{+\cdot}$)(ClO$_4$)] (TMP = tetramesitylporphinate dianion), which range from 28 at 23 °C to 360 at −30 °C ($\Delta E_a = 7$ kcal mol^{-1}; $A_H/A_D = 0.025$ ($\ln A_H = 8.6$ and $\ln A_D = 4.9$)).[14]

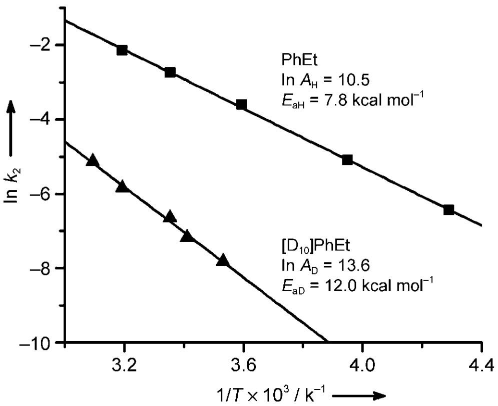

Figure 1. Temperature dependence of the rate constants for the reactions of **2** with PhEt (squares) and [D$_{10}$]PhEt (triangles).

A determination of the KIEs for the oxidation of a series of substrates with a range of C–H bond dissociation energies (D(C–H)) by **1** and **2** revealed a rather surprising pattern (Figure 2; these experiments were carried out at 40 °C to shorten reaction times). For substrates with D(C–H) less than 93 kcal mol^{-1} such as dihydroanthracene (DHA), Ph$_3$CH (TPM), toluene (PhMe), and THF, the KIEs are nonclassical, as reported earlier for PhEt,[6] while the KIEs for substrates with stronger C–H bonds such as MeOH, CH$_2$Cl$_2$, and cyclohexane were smaller (4–8) and fell into the classical range. A value of 4 was also found for the slow decay of **2** in MeCN and [D$_3$]MeCN. This unusual dependence of KIE on D(C–H) is unique.

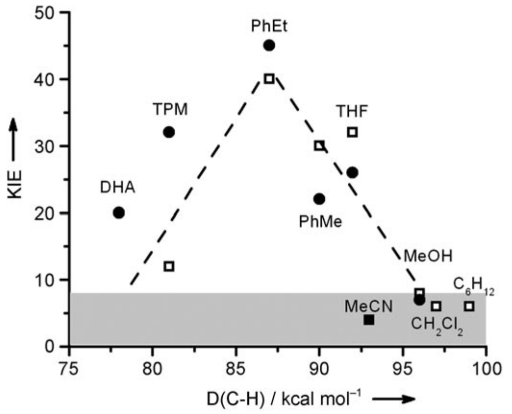

Figure 2. Plot of KIE values versus D(C–H) for **1** (filled circles) and **2** (open squares). The filled square represents the KIE value for MeCN as estimated from the $t_{1/2}$ value of **2** in MeCN and [D$_3$]MeCN. The shaded area represents KIE values within the semiclassical limit, while the dashed lines highlight the rising and falling trends of the KIEs as a function of the C–H bond dissociation energy.

A potentially similar relationship has been reported in only one other system capable of H-atom abstraction.[15] The reaction of the phthalimide *N*-oxyl radical (PINO) with a similar set of substrates also showed a dependence of KIE on D(C–H) with values of 11–13 for the weaker C–H bonds of benzhydrol and fluorene and values of 24–27 for the stronger C–H bonds of PhEt, PhMe, and cyclohexane. Indeed the maximum KIE was observed when the overall reaction free-energy change was close to zero, as expected by the classical Melander–Westheimer explanation for the variation of semiclassical KIE with free energy changes during H-abstraction.[16] However, in the cases of the reactions of **1** and **2** with substrates, the reactions are all exothermic, and this same principle cannot be applied. Furthermore, the large KIE values observed for the reactions of **1** and **2** are for the substrates that have weaker C–H bonds, and hence more exothermic reactions. This behavior is clearly not that expected from semiclassical trends in KIE; we therefore turned to calculations to provide a way to rationalize the D(C–H) dependence of KIE for **1** and **2**.

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Since the reactions of PhEt figure prominently in the KIE plots above, we calculated this reaction with **1**, at the common level used for the cases in previous studies, namely B3LYP/B1 (B1 is LACVP) for characterizing the C–H activation mechanism. The energy was corrected by using a larger basis set, B2 (B2 is LACV3P++**), and solvent corrections (using the solvent parameters for CH_3CN). Like in all previous cases,[9,10] we also found a two-state-reactivity (TSR) scenario (see Figure 3 and the Supporting Information).

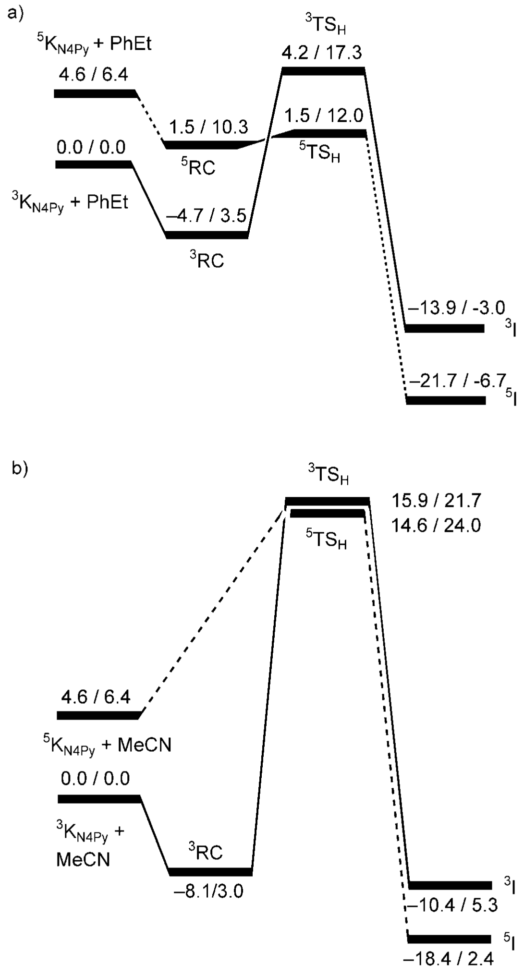

Figure 3. Energy profiles for the reactions of **1** (labeled as K) with a) ethylbenzene and b) acetonitrile.[9b] The relative energies (in kcal mol^{-1}) of each species correspond to the B2//B1+ZPE gas phase value followed by a solvent-corrected value B2//B1+ZPE +solv. RC is a cluster of the reactants, which is stable only in the gas phase. $^{2S+1}$I corresponds to the $Fe^{III}OH/R^{\bullet}$ intermediate with triplet or quintet spin.

Table 1: Semiclassical KIEs calculated by DFT (B3LYP/B1).

Reaction[a]	KIE(T)[b]	KIE(Q)[b]	Observed KIE for **1** (**2**)[c]
K_{N4Py} + C_6H_{12}	6.8	1.9	– (–)
K_{N4Py} + PhMe	5.9	1.4	22 (30)
K_{N4Py} + MeCN	6.7	5.4	– (4)
K_{N4Py} + PhEt	6.4	1.4	45 (40)
$K_{Bn-TPEN}$ + C_6H_{12}	6.8	2.7	– (6)

[a] C_6H_{12} = cyclohexane. Calculations at the B3LYP/LACVP level. KIEs were calculated using the free energy difference between $^{3,5}TS_H$ and ^{3,5}R ($^{3,5}K_{N4Py}$+substrate). The reacting H atom was replaced by D. [b] Semiclassical values. [c] KIE values determined at 40 °C in [D_3]MeCN, except for MeCN, which was obtained from the $t_{1/2}$ values of **2** in MeCN and [D_3]MeCN.

The semiclassical KIE values calculated for the H-abstraction reactions of **1** and **2** with different hydrocarbon substrates are listed in Table 1. It is seen that the semiclassical values on the triplet surface are generally larger than those on the quintet surface. For each spin manifold, the smallest values are calculated for the substrates with the weakest C–H bond, namely PhEt and then PhMe. The quintet state KIE(Q) values for PhEt and PhMe are only slightly larger than 1. Small tunneling corrections based on Wigner's formula do not change these trends and do not affect the KIE(Q) values for PhEt and PhMe at all (see the Supporting Information). Similar results were obtained by de Visser for the C–H activation by the model iron oxo species of TauD.[17] Importantly, the only semiclassical values that seem to match the experimental ones are those for the substrates with the stronger C–H bonds, that is, C_6H_{12} and MeCN. Otherwise, the calculated KIEs show the expected trend[18] from semiclassical values, namely generally larger KIEs for higher barriers and stronger C–H bonds (e.g., compare the values for C_6H_{12} and PhEt). Thus, the very small KIE(Q) values are in line with the very small barriers on the quintet surface, and the larger KIE(T) values are in line with the larger triplet barriers.[18] Clearly, however, these semiclassical values in Table 1 account for neither the trends nor the very large KIE values in Figure 2 above. Furthermore, the very small semiclassical KIE(Q) values are in clear disagreement with the experimental KIE(Q) value (greater than 37) for TauD, for which the oxoiron(IV) oxidant has a quintet ground state[4] that is responsible for the C–H bond activation.[17]

We next investigated the exact kind of tunneling that the experimental data in Figure 2 may correspond to. Traditional tunneling through a single barrier is generally expected to be more efficient as the barrier becomes narrower and to occur through the thinner part of the barrier.[19,20] Assuming that the area under the barrier is conserved in a series of substrates that react with the same iron oxo reagent, then larger H-abstraction barriers will have thinner cross-sections than smaller ones. Thus, under this assumption, in tunneling through a single barrier one can arguably expect the tunneling to increase as the barrier increases. Since the H-abstraction barrier is known to increase as the C–H bond strength increases,[6,21] one might have expected that the KIE tunneling value will increase as the C–H bond becomes stronger. This is manifested in the left-hand branch of Figure 2, but is not true for the right-hand branch of the data set; here, the largest KIE value is observed for PhEt, which has the weakest C–H bond, and normal semiclassical-type values are measured for the substrates that have the strongest C–H bonds.

To formulate a possible tunneling scenario that can serve as a working hypothesis, the energy profiles for two extreme cases, the reactions of $[Fe^{IV}(O)(N4Py)]^{2+}$ with PhEt and

MeCN, are shown in Figure 3. Inspection of the gas-phase energetics (the left-hand data in each pair) shows that, in each case, the triplet surface starts as the ground state but is crossed over by the quintet state. The triplet energy profiles in both cases are steeper than the quintet profiles, but the barriers for H-abstraction from MeCN are considerably higher than those from PhEt, in agreement with experimental data.

Since the triplet barrier shown in Figure 3 is generally higher than the quintet barrier, the crossing of the quintet surface through the triplet barrier could afford a mechanism that behaves like a tunneling process.[9a,10b] However, as shown in Figure 3, this mechanism depends strongly on the substrate. Thus, in the case of MeCN, the quintet energy profile itself is quite steep even in the gas phase, while in the case of PhEt the quintet energy profile is essentially flat. In fact, the ^5TS_H species in the case of PhEt is lower in energy than the onset of the reactants on the quintet surface. Therefore, the amplitude of the C–H vibration explores the entire region from the reactants to the transition state and beyond to the intermediate ^5I on the surface of PhEt. Consequently, during the crossover of the reaction complex from the triplet to the quintet surface, the C–H vibration amplitude on the quintet surface will propagate the complex directly to the intermediate ^5I, and through the triplet barrier, which results in tunneling behavior. On the other hand, [D_{10}]PhEt will have a quintet energy profile with a barrier, so the C–D vibration will not suffice in this case to propagate the reaction complex directly to the intermediate. Thus, whenever the quintet energy profile is very flat, a very large KIE value would be expected. The observation of large KIE(Q) for TauD, as well as the calculations of de Visser,[17] which reveal a very flat quintet surface for the H-abstraction reaction of the quintet state, provides further support for this hypothesis.[22]

In contrast to the flat quintet surface in the case of PhEt, the quintet profile for the reaction with MeCN is rather steep, with a net barrier of 10 kcal mol^{-1} in the gas phase. This barrier is well above the energy stored in the C–H vibration, and therefore the T–Q crossover and the reaction on the Q surface will proceed in a normal barrier-climbing fashion, thus leading to a normal (semiclassical) KIE value.

Our working hypothesis does not depend on the probability of spin crossover, but rather on the shape of the quintet energy curve. Although we cannot make definitive specific predictions for other substrates, we can outline trends. Thus, if the barrier on the quintet surface is larger than the zero-point energy stored in the C–H bond that undergoes activation, the reaction on the quintet surface, after T–Q crossover, will behave as a regular barrier-climbing reaction and lead to a normal KIE in the semiclassical regime, whereas a quintet surface flatter than or equal to the zero-point energy stored in the C–H bond will give rise to tunneling-like behavior, since the C–H vibration will explore a wide range of the quintet potential surface and will propagate the system to the product. Since the H-abstraction barriers are generally proportional to the C–H bond dissociation energies (D(C–H)), with a proportionality constant of around 0.3,[21] this suggests that the tunneling behavior should be observed in a narrow range of D(C–H) values, with a rather abrupt drop as the D(C–H) further increases. This seems to be the general appearance of Figure 2.

Another factor that influences the tunneling behavior is the solvent reorganization. As can be seen in Figure 3, solvation raises the barriers by 4–7 kcal mol^{-1}, which means that the tunneling behavior should occur prior to solvent reorganization. In turn, the solvent reorganization might exhibit additional KIE because of barrier narrowing,[20a] or to a frictionlike mechanism that will depend on the nature of the solvent.[23]

In conclusion, the mononuclear, nonheme oxoiron(IV) complexes **1** and **2** are capable of oxidizing hydrocarbon substrates over a wide range of D(C–H) values. The rate dependence of these reactions on D(C–H) suggests a mechanism of H-atom abstraction. This mechanistic proposal is supported by the deuterium kinetic isotope effect that is observed for each substrate studied, including the reaction with the solvent, acetonitrile. For some of the substrates examined, specifically those with a D(C–H) value less than about 93 kcal mol^{-1}, large, nonclassical values of k_H/k_D are observed. Such large KIEs suggest a mechanism of hydrogen tunneling, which is also supported by other data. This behavior is interpreted by using the TSR concept: the C–H vibration amplitude propagates the molecular complex from the reactant-like geometry directly to the product whenever the quintet energy surface is equal to or flatter than the zero-point energy stored in the C–H bond (Figure 3 a) that undergoes activation. Thus, the TSR concept provides a rationale and a working hypothesis for a substrate-dependent tunneling mechanism that varies nonintuitively with the C–H bond dissociation energy.

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