

## Reaction Mechanisms

## Activation Parameters as Mechanistic Probes in the TAML Iron(V)– Oxo Oxidations of Hydrocarbons

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**Abstract:** The results of low-temperature investigations of the oxidations of 9,10-dihydroanthracene, cumene, ethylbenzene,  $[D_{10}]$ ethylbenzene, cyclooctane, and cyclohexane by an iron(V)–oxo TAML complex (**2**; see Figure 1) are presented, including product identification and determination of the second-order rate constants  $k_2$  in the range 233–243 K and the activation parameters ( $\Delta H^{\pm}$  and  $\Delta S^{\pm}$ ). Statistically normalized  $k_2$  values (log  $k_2'$ ) correlate linearly with the C–H bond dissociation energies  $D_{C-H}$ , but  $\Delta H^{\pm}$  does not. The point for 9,10-dihydroanthracene for the  $\Delta H^{\pm}$  vs.  $D_{C-H}$  correlation lies markedly off a common straight line of best fit for all other hydrocarbons, suggesting it proceeds via an alter-

## Introduction

TAML activators such as 1 (Figure 1) were designed at Carnegie Mellon University (CMU) to be functional replicas of peroxidase and cytochrome P450 enzymes.<sup>[1-4]</sup> In iron TAML systems, multiple  $Fe^{IV}$  derivatives in aqueous solutions<sup>[5,6]</sup> and iron(V)-oxo species in organic nitriles<sup>[7]</sup> are readily accessible. The TAML iron(V)-oxo complexes resemble the active sites of peroxidase and cytochrome P450 oxidase enzymes.<sup>[8,9]</sup> The reactivity studies that have since followed have all been founded on detailed analyses of the spectroscopic properties of TAML iron(III), -(IV), and -(V) species, especially when generated from 1 by metachloroperoxybenzoic acid (mCPBA) in acetonitrile at -40 °C.<sup>[10]</sup> The elementary reactions,  $Fe^{III} \rightarrow Fe^{IV}$ ,  $Fe^{IV} \rightarrow Fe^{V}$ ,  $Fe^{V} \rightarrow Fe^{IV}$ , and the  $Fe^{III} + Fe^{V}$  comproportionation, were first mapped quantitatively as prerequisites to substrate reactivity studies. Then the first substrate oxidations were focused on the conversion of organic sulfides to the corresponding sulfoxides. The expected high reactivity of TAML iron(V)-oxo complexes was confirmed and substrate-controlled electron and oxygen-atom transfer mechanisms were revealed.<sup>[10]</sup> Following this work three years ago, we began a thorough investigation of the reactivity of

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the iron(V)-oxo species toward hydrocarbons.<sup>[11]</sup> While this project was being conducted, as fully reported here, related studies were carried out by two other research groups. Firstly, Sen Gupta and co-workers conducted a kinetic investigation of the oxidation of hydrocarbon C-H bonds by a room temperature stable, Generation V TAML iron(V)-oxo complex 3.<sup>[12]</sup> Then, Nam et al. reported on the kinetics and mechanism of oxidation of hydrocarbons by  $2_{i}^{[13]}$  duplicating the exact study that we have been engaged in for several years. The approaches employed, the reaction conditions selected, the features of the experimental work emphasized, and the foci of the two investigations have turned out to be different such that in this report we will attempt to integrate the combined findings into an optimal mechanistic assessment. The Nam group's study and this work were performed at different temperatures-the Nam group selected 0 °C whereas we collected our data in the temperature range from -40 to -30 °C. This discrepancy impacts the observed chemistry. The stability of 2, which spontaneously undergoes reduction,  $Fe^{V} \rightarrow Fe^{IV[10]}$  is considerably higher at the lower temperatures, such that kinetic data collected by monitoring the  $Fe^V{\rightarrow}Fe^{IV}$  transformation at  $0\,{}^\circ C$  for slow  $C{-}H$ oxidations could be affected by the spontaneous reduction; we examine this difference in this work. Rate measurements at different temperatures as reported herein allow for the determination of the activation parameters,  $\Delta H^{\dagger}$  and  $\Delta S^{\dagger}$ . These parameters are particularly useful for revealing intimate mechanistic details and for integrating the results from the different research groups. Herein, we establish the importance of tunneling in the C-H bond oxidation by 2, which significantly controls the processes at lower temperatures.

Figure 1. Structures of TAML complexes mentioned in this work: iron(III) TAML 1, iron(V)–oxo complex 2, synthesized from 1 and used in this study, and its previously investigated analogue 3.<sup>[12]</sup> The diiron(IV)-µ-oxo dimer 4 is the comproportionation product of 1 and 2.

## **Results and Discussion**

#### Products

Complex 2 was generated ( $\geq$ 95% yield) in acetonitrile at -40 °C by treating 1 with one equivalent of mCPBA.<sup>[10]</sup> Using just one equivalent is important because, in this case, all the oxidant should be consumed by the oxidation of  $Fe^{III}$  to  $Fe^{V}$ . This eliminates potential complications while collecting kinetic data by following the reduction of Fe<sup>V</sup>. From this point of view, our approach is more advantageous than that used by Nam and co-workers, who employed three equivalents of mCPBA, reporting its complete consumption.<sup>[13]</sup> When generated at  $-40^{\circ}$ C, **2** is notably more stable than at 0°C, but still reacts with the hydrocarbons 9,10-dihydroanthracene (DHA), cumene, ethylbenzene, cyclooctane, and cyclohexane at rates that are convenient for kinetic measurements. The hydrocarbons were oxidized to the corresponding alcohols and ketones. Cumene gave a mixture of 2-phenyl-2-propanol and acetophenone. Cyclic alkanes were oxidized to the corresponding cyclic alcohols and ketones. Ethylbenzene afforded 1-phenylethanol  $(83\pm2\%$  yield) and acetophenone  $(16\pm4\%$  yield), based on a Fe<sup>V</sup> to Fe<sup>IV</sup> transformation. Interestingly, the Nam group also reported the formation of styrene and markedly higher amounts of acetophenone,<sup>[13]</sup> which may be associated with the use of three equivalents of mCPBA in the generation of 2. When ethylbenzene was oxidized in the presence of H<sub>2</sub><sup>18</sup>O (0.2 % v/v), no measurable incorporation of <sup>18</sup>O was detected in either the products 1-phenylethanol or acetophenone, despite the fact that 2 is known to undergo a rapid oxygen exchange with water.<sup>[7]</sup> When Nam and co-workers used H<sub>2</sub><sup>18</sup>O, the product 1-phenylethanol underwent 15% <sup>18</sup>O incorporation<sup>[13]</sup> which maybe a consequence of different temperatures employed. However, the lack of <sup>18</sup>O in products generated in the presence of H<sub>2</sub><sup>18</sup>O in our study suggests rapid coupling of O<sub>2</sub> with alkyl radicals produced upon H-atom abstraction by 2; indeed, both the studies by Sen Gupta and co-workers and Nam and co-workers found differing product distributions when O<sub>2</sub> was eliminated. There was a case where the reaction product did not contain oxygen; 9,10-dihydroanthracene afforded a mixture of anthracene (32% yield) and anthrone (65% yield). In general, the product profiles in our study agree with the mechanism shown in Scheme 1, in which an alkyl radical and Fe<sup>IV</sup>–OH are produced in the rate-limiting step with

$$\mathsf{Fe^{V}=O+H-CR_{3}} \xrightarrow{\mathsf{slow}} \mathsf{LFe^{V}-OH+\cdot CR_{3}} \xrightarrow{\mathsf{LFe^{V}=O \text{ or }O_{2}}} \mathsf{LFe^{IV}-OH+\text{ oxidized products}}$$



the rebound process not occurring, consistent with the conclusions of the Sen Gupta and Nam studies.  $^{\scriptscriptstyle [12,13]}$ 

#### **Kinetic data**

Naturally, the oxidation of hydrocarbons by **2** occurs more slowly at -40 °C than at 0 °C. Therefore the kinetic data could be collected by accurately measuring initial rates of the disappearance of **2** at 630 nm (see the Supporting Information for details). In contrast, Nam and co-workers applied an exponential fitting of the entire kinetic curves making no correction for the spontaneous reduction of Fe<sup>V</sup> to Fe<sup>IV.[13]</sup> Ethylbenzene was chosen as a representative substrate. Figure 2A shows the spectral changes that occur on its addition to the solution of **2** at -40 °C. The hydrocarbon reduces Fe<sup>V</sup>, forming Fe<sup>IV</sup>, which was characterized by Nam and co-workers as the monomeric [Fe<sup>IV</sup>(TAML)(mCBA)]<sup>-</sup> (mCBA = meta-chlorobenzoic acid) species (**5**) with the isosbestic points at 560 and 713 nm. The data in Figure 2A reveal similar spectral changes.

In this study, the initial rates were acquired both by observing the disappearance of Fe<sup>V</sup> and the generation of Fe<sup>IV</sup> (see the Supporting Information). There is perfect agreement between the two methods (Figure 2B and Supporting Information). The range of concentrations employed for ethylbenzene and **2** were, respectively,  $(0.49-30.0) \times 10^{-3}$  M (Figure 3A) and  $(0.44-4.4) \times 10^{-4}$  M (Figure 3B). The linear plots found in both cases support the rate law of Eq. (1), in agreement with the findings of Nam and co-workers.<sup>[13]</sup>

$$-d[\mathbf{2}]/dt = k_2 \ [\mathbf{2}][hydrocarbon] \tag{1}$$

Similar plots were observed for reactions of **2** with all hydrocarbons studied. The rate constants  $k_2$  for ethylbenzene (as well as for other hydrocarbons including [D<sub>10</sub>]ethylbenzene) were measured at different temperatures ranging from -40 to -30 °C (see the Supporting Information). Although a broader temperature range is preferred for calculating the activation



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Figure 2. A) Spectral changes associated with reduction of 2 by ethylbenzene. Data points were collected every 15 s and spectra are shown for 90 s intervals. The inset shows the decrease in absorbance at  $\lambda = 630$  nm; B) matching consumption of  $Fe^{V}$  and formation of  $Fe^{IV}$  (see the Supporting Information). Conditions:  $[2] = 2.16 \times 10^{-4} \text{ m}$ , [ethylbenzene] =  $5 \times 10^{-3} \text{ m}$ ,  $[H_2O] = 0.2\%$  (v/v), CH<sub>3</sub>CN, -40°C.

parameters, practical constraints (see the Supporting Information) limited the temperature range used to 10 °C. The rate constants  $k_2$ , calculated from plots such as that in Figure 3A, together with the corresponding activation parameters ( $\Delta H^{+}$ 

Figure 3. Initial rates of reduction of 2 by ethylbenzene as a function of [ethylbenzene] (A) and [2] (B). Conditions:  $[2] = 2 \times 10^{-4} \text{ M}$  (A), [ethylbenzene] =  $4.9 \times 10^{-3}$  M (B), 0.2 % H<sub>2</sub>O (v/v), CH<sub>3</sub>CN, -40 °C.

and  $\Delta S^{\pm}$ ) obtained from the linear ln( $k_2/T$ ) vs.  $T^{-1}$  plots (see the Supporting Information) are collected in Table 1. The products  $k_2$ [hydrocarbon] at -40 °C were all larger than the rate constant for self-decay  $k_{\rm decay}$  of **2**  $(1.0 \times 10^{-5} \, {\rm s}^{-1})^{[10]}$  under the same conditions, to ensure no competition from self-decay. Also, the

1	2	3	4	5	6	7	8	9
Substrate	k₂ [M <sup>-1</sup> s <sup>-1</sup> ] (−40 °C)	$\Delta H^{+}$ [kJ mol <sup>-1</sup> ]	$\Delta S^+$ [JK <sup>-1</sup> mol <sup>-1</sup> ]	k₂ [M <sup>-1</sup> s <sup>-1</sup> ] (0 °C) <sup>[a]</sup>	k₂ [M <sup>−1</sup> s <sup>−1</sup> ] (0 °C) <sup>[13]</sup>	k₂ [M <sup>−1</sup> s <sup>−1</sup> ] (25 °C) <sup>[a]</sup>	k₂ [M <sup>-1</sup> s <sup>-1</sup> ] (25 °C) <sup>[12]</sup>	D <sub>с–н</sub> [kJ mol <sup>–1</sup> ]
9,10-dihydroanthracene	230(2) <sup>[b]</sup>	$19\pm2$	$-117 \pm 7$	1150	-	2400	-	326
cumene	0.091(1)	$14.1\pm0.5$	$-202\pm2$	0.31	0.22	0.55	0.79	354
ethylbenzene	0.145(1)	$25\pm1$	$-153 \pm 6$	1.14	0.45	2.94	0.28	364
[D <sub>10</sub> ]ethylbenzene	0.00566(4)	$39\pm3$	$-119 \pm 15$	0.13	0.04	0.54	-	-
cyclooctane	0.0457(4)	$39\pm3$	$-100\pm10$	1.05	0.72	4.34	-	385
cyclohexane	$2.59(4) \times 10^{-4}$	$60\pm10$	$-70 \pm 40$	0.0295	0.37	0.25	0.022	416

**T** | | **A** | **D** |

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rate vs. hydrocarbon concentration had no significant positive intercept (e.g., Figure 3A), which contributions from the self-decay of **2** would necessarily produce.

#### **Reactivity comparisons**

The availability of enthalpies of activation  $\Delta H^{\dagger}$  (Table 1) presents an opportunity to compare the values of the rate constants  $k_2$  obtained by Nam et al. at  $0^{\circ}C^{[13]}$  with those reported in this work at lower temperatures and to assess the comparative reactivity of complexes 2 and  $3^{[12]}$  where the data for 3was obtained at 25 °C. Therefore the rate constants  $k_2$  in Table 1 were extrapolated to both 0 and 25 °C. The corresponding  $k_2$  values are shown in Table 1 where the  $k_2$  values obtained by Nam et al. and Sen Gupta et al. are displayed as well. For all but one hydrocarbon (cyclohexane), our extrapolated rate constants are reasonably consistent with the results reported by Nam and co-workers.<sup>[13]</sup> The fact that in all cases their rate constants, obtained by measuring the disappearance of Fe<sup>V</sup>, are lower than ours may indicate that the expected regeneration of  $Fe^{V}$  from the  $Fe^{IV}$  product by the excess *m*CPBA for generating 2 in situ is indeed occurring in their study. It is also possible that some or all of the small differences may arise from the tunneling effect (see below). The rate constants for cumene, ethylbenzene, and cyclooctane oxidation are similar (cf. columns 5 and 6 in Table 1). However, our value of  $k_2$ for cyclohexane is lower by more than an order of magnitude. This discrepancy is to be expected based on our knowledge of the instability of 2 at 0°C; the spontaneous decomposition will intrude to measurably reduce [Fe<sup>v</sup>] when the oxidation of less-reactive molecules such as cyclohexane is being followed to artificially increase the observed rate constant.

It is also interesting to compare the reactivity of complexes **2** and **3** with respect to hydrocarbon C–H bonds. Complex **3** is considerably more stable than **2** in MeCN under ambient conditions, that is, the spontaneous  $Fe^{V} \rightarrow Fe^{IV}$  reduction occurs

more slowly.<sup>[12]</sup> The comparison of columns 7 and 8 in Table 1 shows clearly that ethylbenzene and cyclohexane are oxidized by **2** more than an order of magnitude faster than by **3**. Rather surprisingly, cumene reacts with **2** and **3** at similar rates. This might result from the lower enthalpy of activation  $\Delta H^{\pm}$  for **2**, which for cumene equals just 14 kJ mol<sup>-1</sup>, making the rate of reaction for **2** with cumene remarkably insensitive to temperature.

#### **Activation Parameters**

#### Part 1

The rate constants for C–H bond activation by high-valent iron complexes have been extensively reported, [4, 14-16] but they are much less frequently accompanied by the activation parameters  $\Delta H^{\dagger}$  and  $\Delta S^{\dagger}$ , <sup>[17,18]</sup> bringing additional value to the data in Table 1. The negative entropies of activation  $\Delta S^{\dagger}$  lie in the range of -200 to -70 JK<sup>-1</sup> mol<sup>-1</sup>, supporting a bimolecular rate-limiting step.<sup>[19]</sup> Of particular interest are the low enthalpies of activation  $\Delta H^{\dagger}$  of 14, 19, and 25 kJ mol<sup>-1</sup> for cumene, 9,10-dihydroanthracene, and ethylbenzene, respectively, for which the dissociation energies for the corresponding C-H bonds are 354, 326, and 364 kJ mol<sup>-1</sup>, respectively. Low activation enthalpies such as these tend to be found in enzymatic processes with highly ordered transition states and are accompanied by large and negative activation entropies. Here, the activation entropies are typical of biological reactions. Apparently, the TAML iron(V)-oxo complexes facilitate hydrogen atom transfer from a general population of reactant/substrate orientations.

As found by Nam and co-workers at 0 °C, we found a linear relationship at all studied temperatures (-40 to -30 °C) between log  $k_2'$  and  $D_{C-H}$ , here  $k_2'$  is a variant of  $k_2$  statistically corrected by the number of the weakest C–H bonds (Figure 4A), supporting rate-limiting C–H bond cleavage. It is worth noting that such plots are not linear in all systems. For



**Figure 4.** Log  $k_2'$  at different temperatures (A) and  $\Delta H^{\pm}$  (B) plotted against C–H bond dissociation energies  $D_{C-H}$  of hydrocarbons for reactions with **2**. Rate constants  $k_2'$  are statistically corrected values of  $k_2$  by the number of the weakest C–H bonds. See text for details.

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example, a curved log k vs.  $D_{C-H}$  plot is also known, where the interpretation invoked a potential relationship between the  $\Delta H^{+}$  and  $T\Delta S^{+}$  terms.<sup>[20]</sup>

#### Part 2

In Figure 4A, we compare in the standard manner the rate constants and the bond dissociation energies  $(D_{C-H})$ , where  $D_{C-H}$  is the *enthalpy* of C–H homolytic cleavage at 298 K.<sup>[21]</sup> The plots of log  $k_{2}'$  vs.  $D_{C-H}$  are linear in all three studies with TAML activators,<sup>[12,13]</sup> including this one, as is true for the overwhelming number of cases where oxidizing iron complexes have been studied in this way, giving support to rate-limiting C–H bond cleavage.<sup>[4]</sup> By correlating log  $k_2'$  with  $D_{C-H}$ , non-identical thermodynamic functions (Gibbs free energy of activation vs. enthalpy of homolysis) are being compared where, in fact, one has the option to correlate the enthalpy of activation against the enthalpy of homolysis. The corresponding  $\Delta H^{\pm}$  vs.  $D_{C-H}$  correlation is presented in Figure 4B. In contrast with the log  $k_{2}^{\prime}$  vs.  $D_{\rm C-H}$  plot, the experimental  $\Delta H^{\pm}$  value for 9,10-dihydroanthracene is significantly larger than what would be obtained by linear extrapolation of the  $\Delta H^{\pm}$  vs.  $D_{C-H}$ dependence where linearity holds ( $r^2 = 0.99$ ) for the other hydrocarbons studied in this work. The relatively large positive slope of 0.72 found for the  $r^2 = 0.99$  line supports rate-limiting homolytic C-H bond activation with significant C-H bond elongation in the product-like late transition state. The data in Figure 4B signal that the mechanism for 9,10-dihydroanthracene may be different from the other hydrocarbons. Note that the lines in Figure 4A do not detect this difference. Moreover, for a common mechanism to apply across the entire hydrocarbon series, the value of  $\Delta H^{\dagger}$  for 9,10-dihydroanthracene required to maintain the linearity of the  $\Delta H^{\dagger}$  vs.  $D_{C-H}$  plot would be approximately -4 kJ mol<sup>-1</sup> (indicated by the arrow in Figure 4B). A negative value of  $\Delta H^{\dagger}$  for a bond that is stable under ambient conditions is not physically realistic. The measured value of 19 kJ mol<sup>-1</sup> is physically realistic. It is also worth noting that this study supports a previous assertion by Fertinger, Franke, and van Eldik in a related study that "a close correlation between bond strength and reaction rate...no longer exists".[22]

Further evidence that 9,10-dihydroanthracene follows a different pathway is presented in Figure 5, which demonstrates an isokinetic plot in which all hydrocarbons (including  $[D_{10}]$ ethylbenzene) other than 9,10-dihydroanthracene show a linear correlation between  $\Delta H^{\pm}$  and  $\Delta S^{\pm}$ . Once again, the 9,10-dihydroanthracene point lies significantly off the straight line. In other words, the enthalpy–entropy compensation effect<sup>[23]</sup> holds for all studied hydrocarbons other than 9,10-dihydroanthracene. The slope of the  $\Delta H^{\pm}$  vs.  $\Delta S^{\pm}$  plot gives the isokinetic temperature  $T_{iso}$ , at which the rate constants for all reagents (hydrocarbons in this case) are the same;  $T_{iso} = 310 \pm 30$  K. Importantly, this value is distinctly higher than the temperature range over which the  $k_2$  values were measured (233–243 K), validating that the isokinetic relationship is not an artifact and supporting again a common reaction



**Figure 5.** Correlation between  $\Delta H^*$  and  $\Delta S^*$  for the C–H bond activation of hydrocarbons (including [D<sub>10</sub>]ethylbenzene, C<sub>6</sub>D<sub>5</sub>C<sub>2</sub>D<sub>5</sub>) by **2**. Data are taken from Table 1.

mechanism for all studied hydrocarbons other than 9,10-di-hydroanthracene.  $^{\left[ 23\right] }$ 

#### Kinetic isotope effect and tunneling effects

Nam and co-workers reported a value of 11 for the kinetic isotope effect (KIE;  $k_2^{H}/k_2^{D}$  for ethylbenzene) when measured at 0°C,<sup>[13]</sup> which does not differ much from the "classical value" of the KIE (ca. 8) estimated on the basis of the zero-point energy (ZPE) difference between C–H and C–D bonds of 4.77 kJ mol<sup>-1</sup>  $(1.14 \text{ kcal mol}^{-1})$ .<sup>[19]</sup> However, in the absence of variable temperature studies, Nam and co-workers were unable to establish a convincing case for the possibility of a tunneling effect. At the lowest temperature (-40 °C) of study in this work, the KIE increased to 26 for the ethylbenzene/[D10]ethylbenzene pair (Table 1). At -34 and -30 °C, the KIE values are 22 and 18, respectively. All the values obtained at lower temperatures are much higher than both the KIE obtained at 0°C and the classical value, thereby indicating a tunneling effect in the cleavage of the benzylic C-H bond by 2. Using our data from Table 1 and extrapolating the rate constants  $k_2$  for ethylbenzene and  $[D_{10}] ethylbenzene$  to  $0\,^\circ C,$  the KIE was found to be approximately 9, in acceptable agreement with the value of 11 reported by Nam and co-workers.<sup>[13]</sup>

The role of tunneling effects in the cleaving of C–H bonds by dissimilar agents was, for example, augmented and reviewed several decades ago by Bell.<sup>[24]</sup> There are three key criteria for tunneling effects in terms of the Arrhenius equation  $(k=Ae^{-E_a/RT})$ : i) The KIE  $k_{C-H}/k_{C-D}$  itself; ii) the ratio  $A_{C-D}/A_{C-H}$ , where  $A_{C-D}/A_{C-H} \gg 1$ ,<sup>[24]</sup> and iii) a difference in activation energy  $(\Delta E_a)$  between C–H and C–D substrates greater than the ZPE difference of 4.77 kJmol<sup>-1.[25]</sup> Our data for ethylbenzene and  $[D_{10}]$ ethylbenzene give an  $A_{C-D}/A_{C-H}$  ratio of 62 and  $\Delta E_a$  of 14.23 kJmol<sup>-1</sup> supporting the presence of the tunneling effect. In a forthcoming publication, we will detail a theoretical analysis of the tunneling effect in the TAML systems.



#### General mechanistic comments

The results described herein support the non-rebound mechanism suggested recently by Nam and co-workers (Scheme 1).<sup>[13]</sup> The rebound mechanism is typical of catalysis by cytochrome P450 where the C-H bond homolysis involving iron-oxo reactive intermediates occurs within the confines of the protein pocket that helps to organize the structure of the interaction and protect the radical formed from dissociation and subsequent reaction with O2.<sup>[26]</sup> A protecting pocket is absent in catalysis by 2 and the radical intermediate once produced has a higher probability of being trapped by O<sub>2</sub> than in the case of cytochrome P450. A new source of evidence for rate-limiting hydrogen atom abstraction by 2 is present in Figure 4B. The linear correlation between  $\Delta H^{\dagger}$  and  $D_{C-H}$  for all hydrocarbons except 9,10-dihydroanthracene with a slope of 0.72, which is close to 1, is consistent with a significant C-H bond elongation in the transition state.

#### Pathway for 9,10-dihydroanthracene oxidation

This study has unexpectedly revealed the singular nature of the rate-limiting step for 9,10-dihydroanthracene oxidation. It is worth restating that the evidence for this is not observed in Figure 4A, but instead appears in Figures 4B and 5. Figure 4B is particularly convincing, because it suggests a negative value of  $\Delta H^{\dagger}$  for 9,10-dihydroanthracene, if it were to share a common mechanism with the other hydrocarbons studied. Several mechanistic options for the 9,10-dihydroanthracene oxidation can be reasonably suggested: i) Proton-coupled electron transfer; ii) hydride transfer; iii) a distinct stepwise proton transfer followed by electron transfer. These pathways have been discussed in the literature,<sup>[27-30]</sup> and minor structural variations in the reacting partners and reaction conditions are known to cause distinct mechanistic alterations. Our current data do not allow us to suggest with confidence a detailed nature of the rate-limiting step for 9,10-dihydroanthracene oxidation. The KIE value of 6 for the pair DHA/[D<sub>4</sub>]DHA at -40 °C points to a different mechanism, because it is drastically lower than that for ethylbenzene. It should, however, be mentioned that KIE may depend on the C-H bond dissociation energy and a lower value of KIE has been reported for a substrate with lower  $D_{C-H}$ .<sup>[31]</sup> At present, we can only speculate that, since the hydrogen atom transfer (HAT) mechanism is unlikely for 9,10-dihydroanthracene, there might be a significant contribution from an electron transfer pathway in which an electron moves from the electron-rich hydrocarbon to 2 (Scheme 2). The highest reactivity found for 9,10-dihydroanthracene arises from the rather positive entropic term (Table 1). Less entropy should be lost when the rate-limiting step is an electron transfer from the hydrocarbon than when it is hydrogen atom transfer to 2, as the latter mechanism should require higher ordering of the transition state for C–H cleavage.

The electron and proton transfer should occur in a concerted manner, which is consistent with both the KIE value of 6 and the data in Figures 4B and 5. The sp<sup>3</sup> C-H bonds of DHA are significantly more acidic (p $K_a = 30.3^{[32]}$ ) than those of cumene  $(pK_a=41)^{[33]}$  or cyclohexane  $(pK_a=52)$ ,<sup>[34]</sup> which allows to consider the proton transfer for DHA. The substrate  $pK_a^{[29]}$  and the basicity of the oxo ligand<sup>[30]</sup> can drastically affect the mechanism. The low  $pK_a$  of DHA<sup>[29]</sup> and the basicity of **2** may favor the electron/proton transfer mechanism (Scheme 2). The electron should move from the HOMO of DHA,<sup>[35]</sup> supported by its lowest ionization potential (8.3 eV)<sup>[36]</sup> compared to those for cumene and ethylbenzene (8.6<sup>[37]</sup> and 8.7<sup>[38]</sup> eV, respectively). Thus, although it is known to be particularly difficult to differentiate between the mechanisms mentioned above (see, for example, the recent publication by Usharani and co-workers),  $^{\scriptscriptstyle [39]}$  the experimental data available for DHA is not inconsistent with the pathway in Scheme 2.

# Comparative reactivity of iron-oxo TAML species: $\text{Fe}^{\text{IV}}$ vs. $\text{Fe}^{\text{V}}$

Finally, since Fe<sup>IV</sup> and Fe<sup>V</sup> TAML species are intricately involved in the TAML activator catalytic cycle,<sup>[5]</sup> the reactivity of the  $\mu$  $oxo-(Fe^{IV})_2$  dimer 4 was studied for comparison with that of 2. Since iron(IV) species are less reactive than iron(V) species,<sup>[10]</sup> 9,10-dihydroanthracene, as the most reactive hydrocarbon, was selected. Its addition to a solution of 4 (produced by adding 0.5 equivalents of mCPBA to 1) in acetonitrile at -40 °C resulted in the oxidation of 9,10-dihydroanthracene to anthracene and anthrone (reaction time = 1 h, GC-MS data). The reactivity of 4 was estimated by measuring the initial rates of its decay at 750 nm, as was done previously for sulfide oxidation.<sup>[10]</sup> The initial rates varied linearly with the concentration of 4 (Figure 6A) but leveled off with increasing amounts of 9,10-dihydroanthracene (Figure 6B). This saturation is in agreement with the reversible formation of an adduct between 9,10-dihydroanthracene (DHA) and 4 (K) which collapses into products (k):  $4 + DHA \rightleftharpoons \{4, DHA\}$  K',  $\{4, DHA\} \rightarrow products$  (k). Such a mechanism leads to Equation (2) for the rate of consumption of 4.

$$-\frac{\mathbf{d}[\mathbf{4}]}{\mathbf{d}t} = \frac{k \, K \, [\mathbf{4}] \, [\mathsf{DHA}]}{1 + K \, [\mathsf{DHA}]} \tag{2}$$

The data in Figure 6B was fitted to Equation (2) to obtain  $K = (1.07 \pm 0.03) \times 10^3 \,\mathrm{m}^{-1}$  and  $k = (7.51 \pm 0.06) \times 10^{-5} \,\mathrm{s}^{-1}$ . At low [DHA], -d[4]/dt = kK[4] [DHA] and, for comparison of Fe<sup>IV</sup> and Fe<sup>V</sup> species, the product  $kK = (8.0 \pm 0.2) \times 10^{-2} \,\mathrm{m}^{-1} \,\mathrm{s}^{-1}$  should be compared with the second-order rate constant  $k_2$  for 9,10-dihy-

droanthracene (Table 1). Thus, **2** is more reactive than **4** by a factor of  $2.9 \times 10^3$  (Table 1). The reactivity gap is slightly lower for 9,10-dihydroanthracene than that for the methyl phenyl sul-



Scheme 2. Tentative mechanism of oxidation of 9,10-dihydroanthracene by 2.

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**Figure 6.** Initial rates of reduction of **3** by 9,10-dihydroanthracene as a function of [**4**] (A) and [9,10-dihydroanthracene] (B) in CH<sub>3</sub>CN. Conditions: [9,10-dihydroanthracene] =  $4.0 \times 10^{-3}$  m (A); [**4**] =  $5 \times 10^{-5}$  m (B); 0.2 % H<sub>2</sub>O (*v*/*v*), CH<sub>3</sub>CN, -40 °C.

fide oxidation into methyl phenyl sulfoxide which equals four orders of magnitude.<sup>[10]</sup>

### Conclusions

This study is a logical refinement of the mechanistic portrait for the activation of C–H bonds of hydrocarbons by **2**. It supports the conclusions of Nam and co-workers<sup>[13]</sup> concerning homolytic C–H abstraction without a rebound step and further contributes to the general understanding of hydrocarbon oxidations by high-valent iron–oxo complexes. By performing studies at lower temperatures, a tunneling effect in C–H bond activation by **2** was established that contributes to higher reactivity, particularly below 0 °C. The determination of the activation parameters, particularly of the enthalpies of activation  $\Delta H^{\pm}$ , helped to show that standard correlation of rate constants with bond dissociation energies  $D_{C-H}$  may be misleading for the most general mechanistic conclusions. The  $\Delta H^{\pm}$  vs.  $D_{C-H}$  correlation revealed that 9,10-dihydroanthracene reacts differently to all other hydrocarbons studied and presumably there is a contribution from an electron transfer pathway in the rate-limiting step.

## **Experimental Section**

#### Materials

TAML activator 1 was synthesized as previously described.<sup>[40]</sup> 9,10-Dihydroanthracene was obtained from M. P. Biomedicals and recrystallized from ethanol. 9,9,10,10-[D<sub>4</sub>]Dihydroanthracene was synthesized and purified following an established method.[41] <sup>1</sup>H NMR spectroscopy and GC-MS indicated > 95% deuteration. Ethylbenzene (Fluka, GC standard) and cumene (Fluka, analytical standard) were used as received. Cyclooctane (Aldrich, >99%) and cyclohexane (Sigma–Aldrich,  $\geq$  99.7%) were purified by distillation under reduced pressure. Anthrone and cyclooctanol (both M. P. Biomedicals), anthracene (Aldrich), 1-phenylethanol and cyclooctanone (both Aldrich, 98%), acetophenone (Fluka, GC standard), 2phenyl-2-propanol (Fluka, >98%), cyclohexanone (Acros, 99.8%) extra pure), and cyclohexanol (Sigma-Aldrich, 99% reagent plus) were used as received. meta-Chloroperoxybenzoic acid (mCPBA, Acros Organics, 70-75%) was purified by an established method.[42] Acetonitrile, water, and ethanol (all HPLC grade, Fisher Scientific) were used as received. Isotopically enriched H<sub>2</sub>O<sup>18</sup> (97% <sup>18</sup>O) was supplied by Aldrich.

#### Methods

UV/Vis spectroscopic studies were carried out using an Agilent 8453 diode array spectrophotometer. Low-temperature spectral studies were performed using a liquid-nitrogen-cooled cryostat set-up from UNISOKU Scientific Instruments, Japan. All spectral data processing was performed using the SigmaPlot 10.0 software package. A Bruker 300 MHz instrument was used for <sup>1</sup>H NMR spectroscopy. A Thermo Finnigan gas chromatograph (GC) for detecting the oxidation products was equipped with a Restek Rxi-XLB (30 m, 0.25 mm ID, 0.25 µм) column, a Trace DSQ mass spectrometer, a programmable temperature vaporization (PTV) injector, and a COMBI PAL autosampler (LEAP technologies, CTC Analytics). Ultra pure grade helium (Penn Oxygen & Supply Company, PA, USA) at a flow rate of 1 mLmin<sup>-1</sup> was used as a carrier gas. All GC-MS experiments were performed in the standard electronimpact (EI) ionization mode. Products of hydrocarbon oxidation were confirmed by matching their mass spectra in a reference library and by comparing retention times of products and standards. For quantifying 1-phenylethanol and acetophenone formed from ethylbenzene, temperatures of an injection port and a transfer line were 250 and 300°C, respectively. The ion source was kept at 250 °C. The mass spectrometer was turned on after 4 min during each analysis. The electron ionization mode was applied (70 eV). The sample (1 µL) was injected in a splitless mode. The chromatographic oven temperature was programmed in the following way: Held at 50  $^{\circ}\text{C}$  for 5 min, ramped at 15  $^{\circ}\text{C}$  min  $^{-1}$  to 250  $^{\circ}\text{C},$  ramped at 20  $^\circ\text{C}$  min  $^{-1}$  to 300  $^\circ\text{C},$  and held at 300  $^\circ\text{C}$  for 5 min. Under these conditions, the retention times of 1-phenylethanol and acetophenone were 10.27 and 10.48 min, respectively. GC-MS data was processed with Xcalibur software.

#### Hydrocarbon oxidation procedure

In a typical experiment, appropriate volumes of acetonitrile, water (0.2% v/v), and a stock solution of 1 (1 mm) were added in a quartz cuvette to attain the desired final concentration of 1. The





solution was cooled at -40°C for 10 min. A solution of mCPBA (1 equiv,  $2 \times 10^{-2}$  m in acetonitrile) was added to the cold reaction mixture to generate 2. Completion was determined by the absorbance stabilization at 630 nm ( $\lambda_{max}$  for **2**). The final concentration of 2 was assayed from the previously determined extinction coefficients of **2** (4200  $M^{-1}$  cm<sup>-1</sup> at 630 nm).<sup>[7]</sup> An appropriate volume of the stock solution of the hydrocarbon in acetonitrile (0.02-1.00 м) was then added to the pre-formed 2. Initial reaction rates were determined from the absorbance decay at 630 nm ( $\lambda_{\text{max}}$  for 2; see the Supporting Information). Products produced from ethylbenzene were quantified by quenching the reaction mixture with p- $OMeC_6H_4SCH_3$  (5×10<sup>-2</sup> M), which is approximately 5 orders of magnitude more reactive toward 2 than towards ethylbenzene.<sup>[10]</sup> The products of oxidation of other hydrocarbons were analyzed similarly. The reaction completion time was inferred by observing the stabilization of the band at 630 nm.

**Keywords:** C–H activation · iron · oxidation · oxo species · reaction mechanisms

- [1] T. J. Collins, Acc. Chem. Res. 1994, 27, 279.
- [2] T. J. Collins, Acc. Chem. Res. 2002, 35, 782.
- [3] A. D. Ryabov, T. J. Collins, Adv. Inorg. Chem. 2009, 61, 471.
- [4] A. D. Ryabov, Adv. Inorg. Chem. 2013, 65, 117.
- [5] S. Kundu, M. Annavajhala, I. V. Kurnikov, A. D. Ryabov, T. J. Collins, *Chem. Eur. J.* 2012, *18*, 10244.
- [6] A. Chanda, X. Shan, M. Chakrabarti, W. C. Ellis, D. L. Popescu, F. Tiago de Oliveira, D. Wang, L. Que, Jr., T. J. Collins, E. Münck, E. L. Bominaar, *Inorg. Chem.* 2008, 47, 3669.
- [7] F. Tiago de Oliveira, A. Chanda, D. Banerjee, X. Shan, S. Mondal, L. Que Jr., E. L. Bominaar, E. Münck, T. J. Collins, *Science* 2007, 315, 835.
- [8] A. Ghosh, D. A. Mitchell, A. Chanda, A. D. Ryabov, D. L. Popescu, E. C. Upham, G. J. Collins, T. J. Collins, J. Am. Chem. Soc. 2008, 130, 15116.
- [9] T. J. Collins, C. Walter, Sci. Am. 2006, 294, 82.
- [10] S. Kundu, J. V. K. Thompson, A. D. Ryabov, T. J. Collins, J. Am. Chem. Soc. 2011, 133, 18546.
- [11] S. Kundu, Ph. D. Thesis, Carnegie Mellon University (Pittsburgh), 2012.
- [12] M. Ghosh, K. K. Singh, C. Panda, A. Weitz, M. P. Hendrich, T. J. Collins, B. B. Dhar, S. S. Gupta, J. Am. Chem. Soc. 2014, 136, 9524.
- [13] E. Kwon, K.-B. Cho, S. Hong, W. Nam, Chem. Commun. 2014, 50, 5572.
- [14] G. Xue, C. Geng, S. Ye, A. T. Fiedler, F. Neese, L. Que, Jr., Inorg. Chem. 2013, 52, 3976.
- [15] G. Xue, R. D. Hont, E. Münck, L. Que Jr., Nature Chem. 2010, 2, 400.
- [16] D. Wang, M. Zhang, P. Bühlmann, L. Que Jr., J. Am. Chem. Soc. 2010, 132, 7638.

- [17] M. K. Whittlesey, R. J. Mawby, R. Osman, R. N. Perutz, L. D. Field, M. P. Wilkinson, M. W. George, J. Am. Chem. Soc. 1993, 115, 8627.
- [18] K. Cho, P. Leeladee, A. J. McGown, S. DeBeer, D. P. Goldberg, J. Am. Chem. Soc. 2012, 134, 7392–7399.
- [19] J. H. Espenson, Chemical Kinetics and Reaction Mechanisms, 2nd ed., McGraw-Hill, Inc., New York, 1995.
- [20] X. Wang, S. Peter, M. Kinne, M. Hofrichter, J. T. Groves, J. Am. Chem. Soc. 2012, 134, 12897–12900.
- [21] S. J. Blanksby, G. B. Ellison, Acc. Chem. Res. 2003, 36, 255.
- [22] C. Fertinger, A. Franke, R. van Eldik, J. Biol. Inorg. Chem. 2012, 17, 27.
- [23] R. G. Wilkins, Kinetics and Mechanism of Reactions of Transition Metal
- Complexes, 2nd ed., VCH, Weinheim, 1991.
- [24] R. P. Bell, Chem. Soc. Rev. 1974, 3, 513.
  [25] H. Kwart, Acc. Chem. Res. 1982, 15, 401.
- [26] Cota abusera DAFO, Construme March ania
- [26] Cytochrome P450: Structure, Mechanism, and Biochemistry, 3rd ed. (Ed.: P. R. Ortiz de Montelano), Kluwer Academic/Plenum Publishers, New York, 2005.
- [27] J. R. Bryant, J. M. Mayer, J. Am. Chem. Soc. 2003, 125, 10351.
- [28] I. W. C. E. Arends, P. Mulder, K. B. Clark, D. D. M. Wayner, J. Phys. Chem. 1995, 99, 8182.
- [29] M. J. Zdilla, J. L. Dexheimer, M. M. Abu-Omar, J. Am. Chem. Soc. 2007, 129, 11505.
- [30] T. H. Parsell, M.-Y. Yang, A. S. Borovik, J. Am. Chem. Soc. 2009, 131, 2762.
- [31] E. J. Klinker, S. Shaik, H. Hirao, L. Que Jr., Angew. Chem. 2009, 121, 1317; Angew. Chem. Int. Ed. 2009, 48, 1291.
- [32] A. Streitweiser, Jr., C. M. Berke, K. Robbers, J. Am. Chem. Soc. 1978, 100, 8271.
- [33] E. Buncel, B. Maenon, J. Chem. Soc. Chem. Commun. 1976, 648.
- [34] A. Streitwieser, Jr., W. R. Young, R. A. Caldwell, J. Am. Chem. Soc. 1969, 91, 527.
- [35] A. S. Larsen, K. Wang, M. A. Lockwood, G. L. Rice, T.-J. Won, S. Lovell, M. Sadílek, F. Tureček, J. M. Mayer, J. Am. Chem. Soc. 2002, 124, 10112.
- [36] I. C. Lewis, T. Edstrom, J. Org. Chem. 1963, 28, 2050.
- [37] W. A. Duncan, J. P. Sheridan, F. L. Swinton, *Trans. Faraday Soc.* 1966, 62, 1090.
- [38] J. H. Wengrovius, J. Sancho, R. R. Schrock, J. Am. Chem. Soc. 1981, 103, 3932.
- [39] D. Usharani, D. C. Lacy, A. S. Borovik, S. Shaik, J. Am. Chem. Soc. 2013, 135, 17090.
- [40] C. P. Horwitz, A. Ghosh, U. S. Patent 7,060,818, Carnegie Mellon University, 2006.
- [41] C. R. Goldsmith, R. T. Jonas, T. D. P. Stack, J. Am. Chem. Soc. 2002, 124, 83.
- [42] W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals*, 5th ed., Elsevier Science USA, 2003.

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