Characterization of a Ferryl Flip in Electronically Tuned Nonheme Complexes. Consequences in Hydrogen Atom Transfer Reactivity

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Abstract: Two oxoiron(IV) isomers ($^9\text{a}$ and $^9\text{b}$) of general formula [Fe$^{IV}$(O)(PyNMe$_3$)(CH$_3$CN)]$^{2+}$ are obtained by reaction of their iron(II) precursor with NBu$_4$IO$_4$. The two isomers differ in the position of the oxo ligand, cis and trans to the pyridine donor. The mechanism of isomerization between $^9\text{a}$ and $^9\text{b}$ has been determined by kinetic and computational analyses uncovering an unprecedented path for interconversion of geometrical oxoiron(IV) isomers. The activity of the two oxoiron(IV) isomers in hydrogen atom transfer (HAT) reactions shows that $^9\text{a}$ reacts one order of magnitude faster than $^9\text{b}$, which is explained by a repulsive noncovalent interaction between the ligand and the substrate in $^9\text{b}$. Interestingly, the electronic properties of the R substituent in the ligand pyridine ring do not have a significant effect on reaction rates. Overall, the intrinsic structural aspects of each isomer define their relative HAT reactivity, overcoming changes in electronic properties of the ligand.

Introduction

Oxoiron(IV) compounds have been identified as the active oxidants involved in the catalytic cycle of several nonheme iron-dependent oxygen activation enzymes.[1] A common structural feature of these oxoiron(IV) species is the presence of two non-equivalent cis-labile sites at the iron center, which renders the possibility of the existence of two geometrical isomers.[2,3] This is in stark contrast with heme sites, where the porphyrin leaves two trans axial positions available.[4] The significance of the existence of geometrical isomers is often disregarded, and may be quite challenging to address because they are expected to have similar spectroscopic properties. Furthermore, isomerization between geometrical oxoiron(IV) isomers, a process known as “ferryl flip”, has been proposed to take place in the reaction mechanism of several α-ketoglutarate dependent dioxygenases such as clavaminke synthase[5] and DNA-repairing AlkB oxygenases.[6] In these cases, isomerization places the reactive oxo group in the proper position for reaction with the substrate.

Exceptionally, Mössbauer spectroscopic studies on nonheme iron dependent halogenases SyrB2 and CytC3 revealed the presence of two interconverting oxoiron(IV)-chloride intermediates directly involved in the aliphatic halogenation of the substrate,[7] which may correspond to structural isomers according to DFT calculations.[8] Overall, geometrical isomerism may be an important aspect defining the reactivity of nonheme oxoiron(IV) species.

Small molecule model complexes may offer a tool to investigate how subtle aspects of the coordination structure of oxoiron(IV) species affect their chemistry.[9,10] Examples of oxoiron(IV) complexes that could exist as different geometrical isomers are exceedingly rare.[11–15] and isomerization mechanisms are poorly understood, an aspect that also applies to enzymatic sites.

Judicious ligand design in coordination complexes can also help to clarify the effect of crystal field (energy difference between spin states), steric and electronic factors that influence the oxidation abilities of oxoiron(IV) complexes. Several studies have addressed the first two aspects in a quite systematic manner.[16–27] On the contrary, studies describing systematic tuning of the ligand electronic properties of the oxoiron(IV), without modifying sterics, are rather scarce and limited to pentadentate ligands.[28]
Results and Discussion

Synthesis of Ligands and Iron(II) Complexes

The new ligands include the electron-rich Me$_2$PyNMe$_3$, and the electron-poor Cl$_2$PyNMe$_3$, Br$_2$PyNMe$_3$, CO$_2$Me$_2$PyNMe$_3$, and CF$_3$PyNMe$_3$ so that the impact of the electron-donating abilities of the pyridine group of the ligand on the reactivity of the oxoiron(IV) species can be evaluated. [Fe$^{	ext{III}}$(CF$_3$SO$_3$)$_2$(6PyNMe$_3$)] complexes (1$^+$) were prepared by reaction of the corresponding ligand with stoichiometric amounts of Fe($^{	ext{III}}$)(CF$_3$SO$_3$)$_2$(CH$_3$CN)$_2$ (see Supporting Information for details) and obtained as crystalline materials.

Figure 1. Structures of 6PyNMe$_3$ ligands, iron(II) complexes (1$^+$) and oxoiron(IV) compounds (22a and 22b) along with the thermal ellipsoid plot (50% probability) for 22a (hydrogen atoms have been omitted for clarity).

We have recently reported oxoiron(IV) species bearing a tetradentate N-based ligand, [Fe$^{	ext{IV}}$(O)(6PyNMe$_3$)-(CH$_3$CN)]$^{2+}$ (1$^2$), formed as a 1:1 mixture of two geometrical isomers (Figure 1).$^{[20]}$ Over time, the less stable isomer (1$^2$2a) converts into the thermodynamically most stable one (1$^2$2b). The two isomers differ also in their reactivity: 1$^2$2a reacts roughly one order of magnitude faster than 1$^2$2b in hydrogen atom transfer (HAT), but it is slightly less reactive in oxygen atom transfer (OAT). This further supports the idea that the position of the oxo group in the coordination sphere of the iron center is important to dictate the reactivity.

In this work this concept is substantiated and generalized for a family of iron(II) complexes [Fe$^{	ext{II}}$(CF$_3$SO$_3$)$_2$(6PyNMe$_3$)] (1$^+$) supported by electronically-tuned 8PyNMe$_3$ ligands (R = MeO, Cl, Br, CO$_2$Me, CF$_3$, Figure 1). The isomerization of the corresponding oxoiron(IV) compounds (1$^+$) has been studied by kinetic and computational methods, putting forward a novel mechanism that may serve as a model for the enzymatic “ferryl flip”. Furthermore, this series of complexes constitutes a unique platform to evaluate the impact of both the position of the oxo group and electronics on the reactivity of oxoiron(IV) compounds. By doing so, the study reveals unexpected trends, whose detailed analysis provides insight into the nature of HAT and OAT reactions.

Kinetics of the Formation and Isomerization of the Oxoiron(IV) Species

As previously reported for 1$^+$, reaction of 1$^+$ with stoichiometric amounts of NBu$_4$IO$_4$ in acetonitrile at $-35\,^\circ$C affords the corresponding oxoiron(IV) species. Thus, upon...
oxidant addition the characteristic UV/Vis features of $^1$ disappear concomitant with the formation of two low intensity absorption bands at $\approx 800$ nm and $\approx 1000$ nm characteristic of $^2$. This process is so rapid that no detailed analysis on the formation of $^2$ could be made. Interestingly, for all the complexes the relative intensity of the two bands changes over time (Figure 3 and Figure S85). Thus, the intensity of the band at 800 nm decreases with coincident increase of the 1000 nm band and an isosbestic point at $\approx 940$ nm appears along this process. By analogy with $^{12}$, these two bands are assigned to two different geometrical o xoiron(IV) isomers whose spectra differ in the relative intensities of both bands. The only structural difference between the two isomers is the position of the o xo and acetonitrile ligands and thus, the process observed by UV/Vis spectroscopy corresponds to the isomerization of one isomer ($^{2a}$) into the other ($^{2b}$) which are initially formed in a c.a. 1:1 mixture. Albeit previous studies with $^{12}$ were carried out in the presence of triflic acid,[29] preliminary experiments showed that addition of small amounts of this acid only led to minor changes in the rate of isomerization, and so all kinetic experiments in the present work were carried out in the absence of acid.

The spectral changes corresponding to the isomerization of $^{2a}$ into $^{2b}$ could be fitted to a single exponential. Experiments at different temperatures were carried out to derive the corresponding activation parameters using the Eyring equation (Table 1). Although in some cases the occurrence of a slower step for the self-decay of $^{2b}$ is evident, this process was not analyzed in detail because it usually exceeded the stopped-flow time scale. The values in Table 1 clearly show that the nature of R causes significant changes in the isomerization rate constants and the activation parameters. The rate constants increase when the donor character of the R substituent increases, and Hammett plots at the different temperatures (Figure 4) show negative slopes within the narrow $-1.1$ to $-1.2$ range, the mean value for all temperatures being of $-1.13(6)$. This negative slope indicates that some positive charge is built at the complex during the isomerization process, which can be considered to result from total or partial dissociation of an acetonitrile ligand. The small values of the activation entropy and the independence of the isomerization rate constant with the acetonitrile concentration in acetonitrile-mixtures (Table S12 and Figure S87) suggest a novel mechanism involving acetonitrile exchange between two different coordination sites in the o xoiron(IV) species. In an effort to further understand the mechanism of the isomerization, the process was monitored by CSI-MS (Cold-Spray Ionization Mass Spectrometry) in the presence of H$_{15}$O, but no $^{15}$O-incorporation into the o xoiron(IV) species was observed along the reaction (Figure S84). This indicates that a putative o xo-hydroxo tautomerism reminiscent of the processes described for previously reported heme and non-heme systems[17,36–38] is not occurring in this case and water is not directly involved in the conversion of $^{2a}$ into $^{2b}$.

The activation parameters in Table 1 show a good isokinetic relationship (Figure S89) but the ordering of the different complexes differs from that of the Hammett parameters. A more detailed analysis (see section 5.2 in the Supporting Information) reveals that the correlation is mainly caused by compensation of errors due to the correlation between the estimates of $\Delta H^r$ and $\Delta S^r$. Unbiased estimates of the activation parameters ($\Delta H^r$ and $\Delta G^r$) were obtained by evaluating the Arrhenius equation at the harmonic mean temperature ($T_h$) and the values of $\Delta G^r$ at $T_h$ are also included in Table 1. The $\Delta G^r$ values are obtained with more precision than the Eyring activation parameters and show a linear dependence with respect to $\sigma_P$ with a slope similar in absolute value to that in the Hammett plot, thus showing that Hammett plots using the experimental rate constants have superior capability to analyze the effect of substituents on the isomerization process than using activation parameters derived from the Eyring equation. In any case, the present results clearly support an isomerization mechanism for the $^{12}$ species that involves acetonitrile exchange between two different coordination sites through a predominantly dissociative interchange mechanism, which

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**Figure 3.** Typical spectral changes observed upon reaction of $^1$ (1 mM) with 1 equiv NBu$_3$O in acetonitrile at $-30$ °C. Only the isomerization phase is shown. The initial phase of the reaction accounting for the fast formation of a 1:1 mixture of $^{2a}$-$^{2b}$ is not shown.

**Figure 4.** Hammett plot for the isomerization of $^{2a}$ into $^{2b}$ complexes: $-40$ °C (black), $-35$ °C (red), $-30$ °C (green), $-25$ °C (yellow) and $-20$ °C (blue).
Table 1: Summary of kinetic data and activation parameters for the isomerization of 2a into 2b in acetonitrile solution.

<table>
<thead>
<tr>
<th>R</th>
<th>$k_{\text{room}}$ [s$^{-1}$]</th>
<th>$\Delta H^\ddagger$ [kcal mol$^{-1}$]</th>
<th>$\Delta S^\ddagger$ [cal K$^{-1}$ mol$^{-1}$]</th>
<th>$\Delta G^\ddagger_{\text{M06L}}$ [kcal mol$^{-1}$]</th>
<th>$\Delta G^\ddagger_{\text{M06L}}^{(\text{H})}$ [kcal mol$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO</td>
<td>0.0535(6)</td>
<td>16.1(5)</td>
<td>3(2)</td>
<td>15.21(1)</td>
<td>15.20</td>
</tr>
<tr>
<td>H</td>
<td>0.0193(2)</td>
<td>13.5(9)</td>
<td>-9(3)</td>
<td>15.69(2)</td>
<td>15.75</td>
</tr>
<tr>
<td>Cl</td>
<td>0.00961(4)</td>
<td>14.3(4)</td>
<td>-7(2)</td>
<td>16.03(1)</td>
<td>16.03</td>
</tr>
<tr>
<td>Br</td>
<td>0.0131(1)</td>
<td>16.1(9)</td>
<td>0(4)</td>
<td>15.97(2)</td>
<td>15.99</td>
</tr>
<tr>
<td>CO$_2$Me</td>
<td>0.00735(5)</td>
<td>18.2(9)</td>
<td>9(4)</td>
<td>16.12(3)</td>
<td>16.08</td>
</tr>
<tr>
<td>CF$_3$</td>
<td>0.00822(6)</td>
<td>12.0(9)</td>
<td>-18(4)</td>
<td>16.24(3)</td>
<td>16.21</td>
</tr>
</tbody>
</table>

[a] Measured at −35 °C. [b] Results obtained by fitting to the Arrhenius equation at the mean harmonic temperature ($T_{\text{hm}} = 243$ K). [c] Value derived from the rate constant at −30 °C. The estimation of the errors is in all cases smaller than 0.01. Note that $T_{\text{hm}}$ (harmonic mean) is slightly lower than the mean temperature (242.95 K vs. 243.15 K).

causes a decrease of the electron density at the metal complex that is better accommodated when the ligand contains donor substituents. The magnitude of this effect is up to 1 kcal mol$^{-1}$ in the $\Delta G^\ddagger$ values that translates to about one order of magnitude in the rate constants.

**Computational Analysis of the Isomerization Mechanism**

The isomerization mechanism for $^{2a}$ MeO$^2$ and CF$_3$$_2$ was modelled in silico for both S=1 and S=2 spin states (see computational details in the Supporting Information). The chosen DFT functional (M06 L) correctly predicts that isomer $^{2b}$H is slightly more stable than $^{2a}$H, which is also in agreement with highly accurate $ab$ initio DLPNO-CCSD(T) results (Table S13). For species $^{2a}$H and $^{2b}$H, S=1 and S=2 spin states are close in energy. This is also true when B3LYP and oB97XD functionals are used (Table S13). However, if only the electronic energy is considered, S=1 states are always the most stable ones for all studied functionals and DLPNO-CCSD(T) $ab$ initio method. On the contrary, the proposed transition states ($^{TS}_{\text{room}}$, see below) are clearly better described as S=2. The DFT Gibbs energy barriers for the isomerization process are 20.4 (MeO$^2$), 21.0 ($^{2a}$H) and 22.0 (CF$_3$$_2$) kcal mol$^{-1}$ (Figure 5). Thus, the DFT barriers reproduce the decrease of the isomerization barrier when the pyridine moiety contains electron-donating groups, in agreement with the Hammett plot (Figure 4). The structure of the transition state corroborates that the isomerization proceeds through a dissociative interchange mechanism, quite similar to that operating for solvent exchange in metal complexes$^{[39, 40]}$ but involving attack by the entering acetonitrile at a different coordination site. This process involves dissociation of the initially bound acetonitrile molecule and coordination of another solvent molecule at a relative cis position, so that both acetonitrile ligands are weakly bound to the iron center in the TS (i.e. Fe-acetonitrile bond lengths >3.2 Å) (Figure 5 and Table S16). Furthermore, the charges on the complex and in both acetonitrile molecules computed for $^{2a}$H and $^{TS}_{\text{room}}$ using the APOST3D program$^{[41, 42]}$ elucidate a positive charge accumulation on the complex of 0.009, 0.014 and 0.025 electrons for R=Me, R=H and R=CF$_3$, respectively (Table S14). Such positive charge accumulation is in agreement with the conclusions derived from the Hammett plot and also suggests a predominantly dissociative exchange mechanism for the isomerization.

Other mechanisms for the isomerization were explored by DFT means, as for instance the out-of-plane rotation of the oxo and acetonitrile groups, or the predominantly associative exchange mechanism$^{[43, 44]}$. None of them was energetically accessible since the former requires the loss of the chelate effect of the PyNMe$_3$ ligand, and the latter requires the formation of an unstable heptacoordinate intermediate.

**Context and Significance of the Isomerization Mechanism**

The mechanisms of geometric isomerization in octahedral coordination complexes have been studied in detail. Examples of geometric rearrangements in oxometal complexes without metal-ligand bond cleavage (twists) are known for molybdenum complexes that serve as synthetic models of molybdenum dependent oxotransferases$^{[45-48]}$ and in a Re$^\text{V}$
The Kinetics of Hydrogen Atom Transfer (HAT)

The kinetics of HAT processes was studied for the reaction of $^{2a}$ and $^{2b}$ with 1,4-cyclohexadiene (CHD) and 9,10-dihydroanthracene (DHA). Fitting of the UVVis spectral changes for the reaction of the mixture of isomers formed at short reaction times requires a kinetic model with two steps, and global analysis of the data indicate that the first step corresponds to the reaction of $^{2a}$ whereas the second one corresponds to isomer $^{2b}$. However, the values of the rate constants for $^{2b}$ were better estimated from sequential-mixing experiments in which the substrate is changed for the reaction of the mixture of isomers formed at (bpy), changes for the reaction of the mixture of isomers formed at.

Table 2: Summary of kinetic data and activation parameters for the reaction of $^{2a}$ and $^{2b}$ with CHD in acetonitrile solution.

<table>
<thead>
<tr>
<th>R</th>
<th>$k_{2a}$ at $-35^\circ\text{C}$ [kcal mol$^{-1}$]</th>
<th>$\Delta H^\circ$ [kcal mol$^{-1}$]</th>
<th>$\Delta S^\circ$ [cal K$^{-1}$ mol$^{-1}$]</th>
<th>$\Delta G_{2a}^{\ddagger}$ [kcal mol$^{-1}$]</th>
<th>$\Delta G_{2a}^{\ddagger}$ [kcal mol$^{-1}$]</th>
<th>$k_{2b}$ at $-35^\circ\text{C}$ [M$^{-1}$ s$^{-1}$]</th>
<th>$\Delta H^\circ$ [kcal mol$^{-1}$]</th>
<th>$\Delta S^\circ$ [cal K$^{-1}$ mol$^{-1}$]</th>
<th>$\Delta G_{2b}^{\ddagger}$ [kcal mol$^{-1}$]</th>
<th>$\Delta G_{2b}^{\ddagger}$ [kcal mol$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>14.0(2)</td>
<td>7.1(6)</td>
<td>21.3(2)</td>
<td>12.14(2)</td>
<td>12.19</td>
<td>2.2(5)</td>
<td>5.1(5)</td>
<td>35.2(2)</td>
<td>13.51</td>
<td>13.51</td>
</tr>
<tr>
<td>H</td>
<td>12.16(2)</td>
<td>12.18</td>
<td>2.3(3)</td>
<td>2.34(3)</td>
<td>3.4(4)</td>
<td>13.62(2)</td>
<td>13.51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>11.99(2)</td>
<td>12.03</td>
<td>2.50(8)</td>
<td>6.2(9)</td>
<td>31.4(1)</td>
<td>13.63(2)</td>
<td>13.69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Br</td>
<td>12.13(1)</td>
<td>12.17</td>
<td>2.5(1)</td>
<td>6.5(6)</td>
<td>29.2(2)</td>
<td>13.57(2)</td>
<td>13.58</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CF$_3$</td>
<td>12.16(1)</td>
<td>12.17</td>
<td>2.75(2)</td>
<td>5.9(2)</td>
<td>31.1(1)</td>
<td>13.50(1)</td>
<td>13.52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO$_2$</td>
<td>12.16(1)</td>
<td>12.17</td>
<td>3.0(2)</td>
<td>6.8(6)</td>
<td>28.2(2)</td>
<td>13.49(1)</td>
<td>13.51</td>
<td></td>
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</table>

[a] Results obtained by fitting to the Arrhenius equation at the mean harmonic temperature ($T_{hm} = 243$ K). [b] Value derived from the rate constant at $-30^\circ\text{C}$. The estimation of the errors is in all cases smaller than 0.01. Note that $T_{hm}$ (harmonic mean) is slightly lower than the mean temperature (242.95 K vs. 243.15 K).

Computational Analysis of the HAT Reactions

DFT calculations were performed to shed some light in the origin of the faster reactivity of $^{2a}$ with respect to $^{2b}$. In particular, we computed the activation barriers for the HAT reaction with CHD as substrate for both $^{2a}$ and $^{2b}$. The reaction Gibbs energy profile was computed for both S$_1$ and S$_2$ spin states (Figure 6a). For species I and II, the predicted relative stability of S$_1$ and S$_2$ states depends on the chosen functional (the ground states are S$_2$ for MO6 L, whereas they are S$_1$ for oB97XD), as both spin states are close in energy. However, TS(II–III) and III are clearly better described as S$_2$ 2 compounds by all the DFT methods tested. The reaction Gibbs energy profile starts with the formation of the reactant complex, which is endergonic due to the entropy contribution, indicating that the reactant complex is not stable. In the following step, the HAT transition state is reached, TS(II–III), which is 1.6 kcal mol$^{-1}$ lower in energy for $^{2a}$ than for $^{2b}$, which is in agreement with the relative values of the experimental rate constants, indicating that HAT is the rate-determining step of the reaction. In all the HAT transition states the substrate approaches sideways (TS Fe–O–H angles for $^{2a}$ and $^{2b}$ are 125° and 138° respectively), thus the reaction proceeds via π-channel, i.e. through the π electron orbital (Figure 6b). We also tried to optimize the o-
channel transition states, but all optimizations led to the angular π-channel HAT TS.

In order to understand the origin of the differences on the HAT chemical barrier of the two isomers, we thoroughly compared the key geometrical parameters of II→2a (TS_{II-a}) and II→2b (TS_{II-b}) involved in the reaction, namely the Fe-oxo, the oxo-H and the H-CHD distances. For II→2a the only substantial difference observed is the oxo-H distance that increases from 2.49 Å in II to 3.29 Å in II→2a, suggesting that the steric repulsion is larger in the latter. To confirm this hypothesis, the noncovalent interactions between the CHD substrate and the PyNMe₃ ligand were analyzed using the NCIPLOT program, which enables the identification of attractive and repulsive interactions based on the real-space analysis of the reduced density gradient (Figure 7). Specifically, in II→2a, the CHD substrate is located parallel to the pyridine ligand and there is a weakly-favorable interaction between them (green NCI surface) promoted by a π-π interaction that facilitates the approach of the substrate to the oxirion moiety. On the contrary, in II→2b there is a repulsive noncovalent interaction between a methyl group of the ligand and the CHD due to the steric clash between them that hampers the approach of the substrate to the oxirion moiety. This steric repulsion in II→2b is the origin of the increase of its HAT activation barrier with respect to II→2a.

The analysis of the geometrical parameters of TS_{II-a} also shows that, in complete agreement with the Hammond-Leffler postulate, II→2a presents an earlier TS_{II-a} than II→2b. In this particular case, the electronic effects play a secondary role as TS_{II-a} and TS_{II-b} have very similar electronic structures (Figure S126).

Temperature Dependence and Hammett Plots of the HAT Reaction Rates

The temperature dependence of the rate constants for the reaction of II with CHD was analyzed in the same way as the isomerization process, and similar comments could be made in this case (detailed Hammett, ΔH° vs. ΔS°, and log k vs. T plots are included in the Supporting Information). Nevertheless, an important comment must be made at this point, as the data (Figure 8) show that the order of the rate constants for the compounds with the different R substituents is strongly temperature dependent, so that the ordering is CO₂Me<H<MeO<Cl<CF₃<Br at −40°C, and Br≈
$\text{CF}_3 < \text{CO}_2\text{Me} \approx \text{H} < \text{Cl}$ at $-20^\circ \text{C}$ for $^2\text{a}$. Thus, quite different conclusions could be derived on the effect of the substituents, thus showing the limitations of kinetic studies at a single temperature.

In contrast, Hammett plots clearly show that the nature of the substituent does not have any significant effect on the kinetics of hydrogen atom transfer. Thus, Figure 9 shows in all cases a slope close to zero. Of notice, the same trend is observed for the two different substrates and, as expected from the close energy of the C–H bonds in CHD and DHA, the plots for both substrates also show close mean values (Table S29).

The lack of impact of the electronic tuning of the PyNMe$_2$ family of oxoiron(IV) complexes in their HAT reactions was unexpected as it was envisioned that enhancing the electrophilicity of the hydrogen abstracting species (oxoiron(IV)) would facilitate the reactions, which should be understood as oxidation processes. Ground state and transition state energetics should be considered to explain the data but it must be kept in mind that HAT reactions by high valent oxometal species frequently display linear free energy correlations that suggest concerted electron and proton transfer. A thermodynamic cycle permits to divide the thermodynamic driving force of HAT in two components; an electrophilicity driving force, arising from the redox potential of the $M^{n+}(O)/M^n(O)$ couple and a basicity driving force arising from the $M^{n+}(O)/M^{n+}(\text{OH})$ pair. Simple considerations regarding electron density at the metal predict that the two effects must respond in opposite directions as the oxometal unit is made more electron-poor, which can be viewed as a thermodynamic compensation. Electrophilicity must obviously increase on going from complexes with electron-rich ligands to electron-poor ones. On the contrary, the basicity of the oxometal unit must decrease. The similarity in the HAT reaction rates among substituents, thus showing the limitations of kinetic studies involved. In the frame of proton coupled electron transfer (PCET), HAT is generally described as the concerted transfer of a proton and an electron from one group to another in a single kinetic step.\[66\] In this case, a certain degree of asynchronicity in the proton and electron transfer may exist, so that proton or electron transfer may exhibit a more dominant role and some charge should accumulate in the substrate during the TS. However, this is not always the case. Indeed, recent work by Borovik and Green\[68\] suggests that oxometal systems exhibiting a strong correlation between log($k$) and $\text{BDE}_{\text{C–H}}$ follow synchronous HAT processes. In the same work, they provide an example in which there is no such correlation and the Hammett analysis shows a strong correlation with the $\sigma_p$ values for the substituents in the substrate with a positive slope that supports an asynchronous PCET. In addition, Srnce and co-workers disclosed that those oxoiron species favoring dissociation over rebound mechanisms after HAT consistently show low degrees of asynchronicity.\[69\] Compound $^2\text{b}$ complies with these two requisites (correlation of reaction rates with C–H bond strength and a preference for dissociation over rebound mechanisms),\[70\] thus supporting the idea that its HAT reactivity is synchronous. We infer that the necessary consequence of this scenario is that positive charge is not effectively built up in the TS of hydrogen atom transfer in $^2\text{b}$. The zero slope in the Hammett plot observed for the HAT reactions of the $^2\text{a}$ and $^2\text{b}$ series of complexes may reflect this situation.

**Computational Analysis of the Asynchronicity of the HAT**

We have used the asynchronicity factor $\eta$ defined by Srnce and co-workers that measures the degree of asynchronicity of $\text{H}'/\text{e}^-$ transfers in HAT in terms of the DFT reduction potentials and acidity constants of the reacting complex-substrate pair.\[71\] The $\eta$ values for $^2\text{a}$ and $^2\text{b}$ are $\eta = 506 \text{ mV}$ and $\eta = 471 \text{ mV}$, respectively, which indicate that both compounds operate through a quite synchronous HAT mechanism (see Supporting Information for further details).

The proposal that the synchronicity of the HAT is the origin of the lack of a Hammett slope is further supported by the different effects observed in the OAT reactions (vide infra), where charge accumulation in the substrate during the OAT results in reactions that are accelerated when the oxometal is made more electrophilic, and slowed down for less electrophilic oxidants.

**The Kinetics of Oxygen Atom Transfer (OAT)**

The effect of the R substituent on the kinetics of OAT processes for $^2\text{b}$ was studied using thioanisole as substrate (see section 7 in the Supporting Information for more details). The rate constants derived for both isomers are quite close to each other, $^2\text{b}$ reacting slightly faster than $^2\text{a}$ (Table S37). The $k_{\text{H}2}/k_{\text{Me}2}$ quotients are in the range 0.56–1.04, which indicates that the rate of reaction of both isomers never differ by more than a factor of 2, which contrasts with the results obtained for HAT processes, in

![Figure 9](https://www.angewandte.org/content/62/33/15213773/F1.large.jpg)
which \( ^22a \) reacts much faster. The values of \( \Delta G^\circ_\text{IS} \) in Table S37 were estimated directly from the rate constants, and they indicate that for a given R the \( \Delta G^\circ_\text{IS} \) difference is quite small (\(< 0.3 \text{ kcal mol}^{-1} \)). For a given isomer the values of \( \Delta G^\circ \) roughly decrease as the \( \sigma_p \) value of the R substituent increases. Actually, the Hammett plots (Figure 10) show a positive slope of 0.8(2) for \( ^22a \) and 0.63(9) for \( ^22b \), which indicate that the oxygen atom transfer occurs through an electrophilic attack of the oxoiron(IV) intermediates to the substrate. The observed positive slope in the Hammett plot was also rationalized by DFT calculations, which confirmed the accumulation of negative charge (\(-0.52 \) electrons for both \( ^22a \) and \( ^22b \) isomers, Table S39) in the transition states of OAT processes, in line with previously studied sulfonation reifications performed by oxoiron(IV) complexes.[71]

**Conclusion**

In this work, a new family of oxoiron(IV) species (\( ^22 \)) containing \( ^2\text{PyNMMe}_3 \) ligands (R = OMe, Br, Cl, CO$_2$Me, CF$_3$) with systematically modulated electronic properties has been described. The \( ^22 \) complexes are initially formed as a mixture of two isomers that differ in the relative position of the oxo group in the iron coordination sphere, but the mixture evolves to complete formation of the thermodynamically favored isomer. Kinetic studies and DFT calculations lead to a mechanistic proposal for the isomerization process involving a dissociative interchange mechanism. The mechanism constitutes a model to explain the “ferryl flip” postulated in several nonheme iron dependent oxygenases. It also illustrates that the oxidant. On the hand, systematic alteration of the electronic properties of the oxoiron(IV) provides insight about the nature of the HAT reaction. Specifically, the resulting Hammett analysis, denoting a practically flat correlation between HAT reaction rates and Hammett parameters, is in stark contrast with typical negative slopes of oxo transfer reactions, providing strong indication that the reaction takes place via a nearly synchronous PCET.

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**Conflict of Interest**

The authors declare no conflict of interest.

**Data Availability Statement**

The data that support the findings of this study are available in the supplementary material of this article.

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