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Do Spin State and Spin Density Affect Hydrogen Atom Transfer Reactivity?

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Abstract

The prevalence of hydrogen atom transfer (HAT) reactions in chemical and biological systems has prompted much interest in establishing and understanding the underlying factors that enable this reactivity. Arguments have been advanced that the electronic spin state of the abstractor and/or the spin-density at the abstracting atom are critical for HAT reactivity. This is consistent with the intuition derived from introductory organic chemistry courses. Herein we present an alternative view on the role of spin state and spin-density in HAT reactions. After a brief introduction, the second section introduces a new and simple fundamental kinetic analysis, which shows that unpaired spin cannot be the dominant effect. The third section examines published computational studies of HAT reactions, which indicates that the spin state affects these reactions indirectly, primarily via changes in driving force. The essay concludes with a broader view of HAT reactivity, including indirect effects of spin and other properties on reactivity. It is suggested that some of the controversy in this area may arise from the diversity of HAT reactions and their overlap with proton-coupled electron transfer (PCET) reactions.

I. Introduction

Hydrogen atom transfer (HAT, eq 1) is one of the most fundamental chemical reactions.¹ It is central to combustion, the

chemistry of reactive oxygen species in biology, the oxidation of organic molecules in the atmosphere and surface waters, and many industrial oxidation processes. HAT has also been recognized to be the key step in many oxidations accomplished by metalloenzymes,² most famously proposed in Groves' rebound mechanism for reactions of cytochrome P450 heme enzymes.³ HAT is also implicated in the catalytic cycles of many non-heme iron enzymes,^{2a, 2d, 2e} including methane monooxygenase.^{2b} The ability of metalloenzyme active-sites, metal complexes, and solid surfaces to abstract hydrogen atoms from substrates has prompted a closer look at the factors that enable this reactivity.^{4,5,6,7}

A much-debated issue in HAT is the importance of unpaired spins: does the spin state of the abstractor and/or the amount of unpaired spin density on the abstracting atom affect reactivity? This is part of a broad discussion of the influence of spin states and spin state

changes on transition metal reactivity, as stated in a recent commentary by Costas and Harvey: "Properties of different spin states will surely continue to serve ... as a guiding principle for molecular design by computational and experimental chemists."⁸

Traditionally, HAT reactions were the province of organic radical chemistry, and unpaired spin is present in all of the classical abstractors, such as halogen atoms, oxyl radicals, and alkyl radicals. There is a common intuition that HAT must be related to spin because so many facile HAT reactions involve radicals. The issue of spin has come to the fore as it has been recognized that transition metal species often react by HAT, or the more general mechanism of proton-coupled electron transfer (PCET). These transition metal active sites, catalysts, and reagents can exist in spin states from singlet to septet, and can exhibit multi-[spin]-state reactivity. It has been suggested that open-shell metal oxidants are inherently better hydrogen atom abstractors, and that singlet ground state molecules need to react *via* higher-spin states. The literature contains many statements such as "From these combined experimental/computational studies, the crucial role of unpaired spin density at the abstracting atom becomes clear."⁷ From a paper about a manganese(V) oxo species: "Oxyl character, found only in the triplet and quintet states, is thus essential for efficient C-H activation".⁹ The arguments for spin playing a key role come from analyses of gas phase reactions, from computational studies, and from valence-bond analyses.^{6,7}

In contrast, extensive studies by Rüchardt have shown that simple closed-shell organic molecules (singlet, $S = 0$) can react by HAT, albeit usually at elevated temperatures. This work is described in an excellent 1997 review.¹⁰ Singlet metal complexes including d^0 permanganate and chromium(VI) compounds have also been shown, in studies starting in the 1960s, to abstract $H^\bullet$ from hydrocarbon substrates.^{11,12} A number of recent reports describe H-atom abstractions by a variety of d^n metal species ($n > 0$) with singlet ground states, including Goldberg's $Mn^V(O)$,¹³ Kojima's 7-coordinate $Ru^{IV}(O)$,¹⁴ and Tolman's $Cu^{III}(OH)$ ¹⁵ complexes.¹⁶

The motivation for this essay is to clarify how spin state and spin density affects HAT reactivity. This understanding should be valuable from the design of new catalysis to studies of metalloenzyme biochemistry. The simple arguments advanced here should be of fundamental interest and of value to experimental chemists in the bioinorganic, inorganic, and organometallic communities.

The next section of this essay uses a simple kinetic/thermodynamic argument to prove that open-shell species cannot in general be intrinsically more reactive than closed-shell species. The common correlation of HAT with free radical chemistry is not a causation. The larger third section presents an analysis of published computational studies of HAT reactions, showing that reactivity correlates better with driving force than with spin state. It provides a context to understand why higher-spin forms often are faster H-atom abstractors and enables predictions of cases where lower spin states should be more reactive. The essay also brings together disparate perspectives, including the suggesting that some of the controversy in this area relates to the diversity of HAT processes. These vary from traditional cases in which the e^- and H^+ originate in the same bond to reactions in which there is some separation between the two particles.

II. A simple kinetic demonstration that unpaired spin cannot be a requirement for HAT reactivity

There are a number of examples of HAT reactions between two closed-shell species, such as $MnO_4^- + Ph_2CH_2$ ($\Delta G^\circ_{HAT} \approx -1 \text{ kcal mol}^{-1}$)^{12c,17} and α -methylstyrene + 9,10-dihydroanthracene ($\Delta H^\circ_{HAT} = +39 \text{ kcal mol}^{-1}$).¹⁰ Such reactions can be written

schematically as in eq 2, in which X: and H–Y are both closed-shell, singlet ($S = 0$) reactants. Neither X: nor H–Y have any significant unpaired spin density on any atom. H-atom transfer gives two doublet ($S = 1/2$) products, indicated by dots in the equation.

The reaction in the forward direction is HAT with a closed-shell abstractor. The reaction in the reverse direction is HAT by the radical species $\text{Y}^\bullet$.

The hypothesis that reagents with unpaired spins are better HAT abstractors requires that the reaction of $\text{Y}^\bullet$, the reverse of equation 2, be more facile than the forward reaction, which has a closed-shell species as the abstractor. However, when the free energy of reaction 2 (ΔG°_2) is zero, *the barriers $\Delta G^\ddagger$ are the same for radical species $\text{Y}^\bullet$ as for the non-radical species X:*. The rate constants for HAT by $\text{Y}^\bullet$ and by X: must be identical ($K_{\text{eq}} = 1$). There can be no kinetic advantage for $\text{Y}^\bullet$ over X: due to it having an unpaired spin. It should be emphasized that in comparing different reactions in which $\Delta G^\circ_2 = 0$, the barrier $\Delta G^\ddagger_2$ may differ (e.g., comparison of $\text{X:} + \text{H}-\text{Y} \rightarrow \text{X}-\text{H}^\bullet + \text{Y}^\bullet$ with $\text{Z:} + \text{H}-\text{Y} \rightarrow \text{Z}-\text{H}^\bullet + \text{Y}^\bullet$). The key point is that for each reaction, the barrier must be the same for both species.

In the more general case when $\Delta G^\circ_2 \neq 0$, the barriers to the forward and reverse HAT reactions differ only by ΔG°_2 (eq 3 and Figure 1). If the reaction of $\text{Y}^\bullet$ is faster (lower barrier) than that of X:, it is due *only* to the reaction of $\text{Y}^\bullet$ being more thermodynamically favorable. *There cannot be any intrinsic kinetic advantage for $\text{Y}^\bullet$ vs. X:*. In this context, an intrinsic kinetic effect is something that affects the kinetic barrier independent of the net thermochemistry of reaction.¹⁸

$$\Delta G^\ddagger_{2r}(\text{HAT by } \text{Y}^\bullet) = \Delta G^\ddagger_{2f}(\text{HAT by X:}) - \Delta G^\circ_2 \quad (3)$$

This simple analysis comparing the forward and reverse reaction rates for eq 2 shows that the spin state or spin density of an active site cannot be the direct determinant of hydrogen atom abstraction reactivity.¹⁹ In general, HAT reaction barriers $\Delta G^\ddagger_1$ can be understood in various ways. From a Marcus theory perspective, the key parameters are the reaction free energy ΔG°_1 and the reorganization energy λ .^{5, 20} The related Valence Bond analysis uses the reaction energy, the resonance energy stabilization of the transition state (B) and the energies required to bring the reactants into resonance with the products at the crossing point ($f_o G_o$).⁶ As emphasized by Shaik,⁶ the spin state of a reactant can affect all of these parameters and therefore indirectly affect the rate of an HAT reaction. For instance, within some sets of radicals those with the larger *spin density* at the abstracting atom may have decreased reorganization energies.⁶ In sum, Figure 1 shows that the intrinsic barriers for HAT by X: and $\text{Y}^\bullet$ in eq 2 must be the same, but the size of this barrier is determined by the properties of the reagents, including the spin on $\text{Y}^\bullet$.

It should be noted that the arguments here and below apply only to HAT reactions that occur in a single kinetic step. Different issues arise for net H-atom transfers that occur in multiple steps, for instance electron-then-proton, or proton-then-electron transfer. Additionally, it is assumed that HAT steps are spin-allowed, that they occur without change in the overall spin state of the system.²¹ Our recent study of the spin-forbidden HAT reaction converting a quartet cobalt(II) complex to a singlet Co(III) product, $[\text{Co}^{\text{II}}(\text{H}_2\text{L})_3]^{2+}$ ($S = 3/2$) + $\text{XO}^\bullet$ ($S = 1/2$) $\rightarrow$ $[\text{Co}^{\text{III}}(\text{H}_2\text{L})_2(\text{HL})]^{2+}$ ($S = 0$) + XOH ($S = 0$), concluded that the reaction occurs in two steps, with equilibrium spin isomerization to the singlet surface prior to HAT.²²

III. Effects of spin state

If the spin state cannot be the primary determinant of HAT reactivity, why is it that reagents with higher spin states are frequently found to be more reactive toward HAT than related species with lower spin states? A complication in such comparisons is that they usually involve different chemical species. For instance, gas-phase studies in the Schwarz laboratory show CaO^{+*} to be much more reactive than neutral, closed-shell CaO .⁷ The HAT rate for a dimeric $\text{Fe}^{\text{IV}}(\text{O})(\mu\text{-O})\text{Fe}^{\text{III}}$ complex with an $S = 2$ $\text{Fe}^{\text{IV}}(\text{O})$ unit is larger than that of a different $[\text{Fe}^{3.5}(\mu\text{-O})]_2$ compound.²³ In these and other examples, the species being compared have different ligands, geometries, electronic structures, and/or charges, so it is difficult to extract solely the effects of the spin state.

A more direct comparison is the HAT reactivity of the same complex in different spin states. Many computational studies of metal-mediated HAT reactions report energy surfaces for multiple spin states, at the same level of theory. While distinct spin states of the same complex have different calculated structures and thermochemistry for HAT, they are more directly comparable than two different species.

A. Barrier and driving force as a function of spin state

A typical example of the many computational studies of transition metal HAT reactions is the energy profile for HAT from cyclohexane to the iron(IV)-oxo complex $[(\text{N4Py})\text{Fe}(\text{O})]^{2+}$, reproduced in Figure 2 ($\text{N4Py} = \text{N,N-bis(2-pyridylmethyl)-N-(bis-2-pyridylmethyl)amine}$, $\text{R-H} = \text{C}_6\text{H}_{12}$).²⁴ As is often found, the higher spin state is higher in energy in the reactant but has a lower barrier to reaction. Thus it would be easy to conclude that the higher spin state is the origin of the higher reactivity. However, as the authors of this study point out,^{24–25} it is also valuable to examine the product energies in addition to those of the reactants and transition states.

Following the Hammond postulate, the position and energy of the transition state usually reflects the free energy change (ΔG°) for a single reaction step.²⁶ For two similar reactions, the more exoergic reaction has a transition state that is more reactant-like, a barrier that is earlier along the reaction coordinate, and a barrier that is lower in energy. For the case illustrated in Figure 2,²⁴ HAT on the triplet surface is calculated to have $\Delta E = +0.1 \text{ kcal mol}^{-1}$, while the reaction on the quintet surface has $\Delta E = -14.3 \text{ kcal mol}^{-1}$. The Hammond postulate then implies – as noted in this study²⁵ – that the quintet surface has an earlier transition state and a lower HAT barrier. The lower barrier on the quintet surface occurs *even if the intrinsic reactivity of the quintet and triplet states are the same*. In this case, the $14.4 \text{ kcal mol}^{-1}$ greater exoergicity of the reaction on the quintet surface more than compensates for the $5.8 \text{ kcal mol}^{-1}$ higher energy of the reactant quintet state.

The preceding example illustrates the importance of driving force ($\Delta G^\circ_{\text{HAT}}$) on HAT reactions. This is not a new conclusion, as it has been well established in the organic radical literature for decades and long been a key part of Shaik's Valence Bond analyses of radical reactivity.^{6, 27} The correlation of barrier height with driving force is sometimes called the Bell-Evans-Polanyi (BEP) principle (from 1938).²⁸ While the BEP correlation does not generally hold for chemical reactivity, it has been found to work well for many kinds of HAT reactions. The BEP correlation was cited in the report of the results in Figure 2.^{24–25}

Our laboratory has further shown that most HAT reactions are well described by a Marcus-theory approach, with rate constants typically well predicted by the Marcus cross relation.^{5, 20b} When comparing two similar reactions (reactions with the same intrinsic barrier λ), this approach predicts that the change in the barrier height $\Delta\Delta G^\ddagger$, upon a change in driving force $\Delta\Delta G^\circ$, is given by equation 4a. For the large majority of HAT reactions that

are in the $\Delta G^\circ \ll 4\lambda$ regime, the Marcus approach predicts that the slope of the BEP correlation, $\Delta\Delta G^\ddagger/\Delta\Delta G^\circ$, sometimes referred to as the Brønsted α , will be close to 0.5. In other words, roughly half of the change in ΔG° will appear in $\Delta G^\ddagger$.²⁹ This is typical of free energy relationships for solution phase reactions.^{26,30} Though this expression was derived using Marcus theory, a very similar expression is obtained from VB theory, following Shaik (eq 4b; E_{rp} = driving force, ΔG_o = promotion energy gap).⁶

$$\Delta\Delta G^\ddagger/\Delta\Delta G^\circ = 0.5 + \Delta\Delta G^\circ/4\lambda \quad (4a)$$

$$\Delta\Delta E^\ddagger_{\text{VB}}/\Delta\Delta E_{\text{rp}} = 0.5 + \Delta\Delta E_{\text{rp}}/\Delta G_o \quad (4b)$$

Applying this analysis to the case shown in Figure 2, the 14.4 kcal mol⁻¹ greater exoergicity for the quintet state over the triplet state predicts a 7.2 kcal mol⁻¹ lower barrier. The reported calculated difference in barriers is 8.1 kcal mol⁻¹, in quite good agreement with the prediction from equation 4. While there could be other differences between the quintet and triplet states that affect the barrier, the primary effect is that the different spin states have different driving forces for H-atom abstraction.

B. A meta-analysis of 13 computational studies

We have analyzed 13 computational papers on HAT reactions iron and manganese oxo complexes from different laboratories to explore the generality of the conclusion that driving force is the major contributor to the observed spin effects.³¹ This is a sort of chemical meta-analysis.³² These 13 are all of the papers found in an initial literature search for studies with the data necessary for the analysis; while this is not a comprehensive set, no active selection was done. The studies are from different laboratories and use a variety of related methods. These papers report the barriers and energetics for H-atom transfers of the same species in different spin states, typically as energies $\Delta E^\ddagger$ and ΔE° (rather than free energies). Some of the papers also compare σ and π transition state energies of the same spin multiplicity. Only in a few cases was the driving force emphasized as a primary determinant of differences between spin states.^{33,25,34}

These 13 papers report calculations for 31 reactions which can be analyzed to give 59 different comparisons of the same chemical process on two different spin surfaces. Each comparison is summarized as a row in Table 1 of Appendix A. The $\Delta E^\ddagger$ and ΔE° for both spin isomers are given, as are the differences, $\Delta\Delta E^\ddagger$ and $\Delta\Delta E^\circ$, between the higher and lower spin state. The ratio $\Delta\Delta E^\ddagger/\Delta\Delta E^\circ$ (Figure 3) then provides a test of the relationship between barrier and driving force (eqs 4).

In 52 of the 59 comparisons, the isomer with the more favorable driving force (ΔE°) has the lower barrier ($\Delta E^\ddagger$), as indicated by a positive value of $\Delta\Delta E^\ddagger/\Delta\Delta E^\circ$. Seventeen of these cases have computed magnitudes of $|\Delta\Delta E^\ddagger|$ and/or $|\Delta\Delta E^\circ|$ of less than 2.5 kcal mol⁻¹ and therefore significant uncertainty in the sign of $\Delta\Delta E^\ddagger/\Delta\Delta E^\circ$. DFT calculations are known to have difficulty in reproducing the relative energies of spin states accurately.²² Omitting these 17 cases leaves 42 comparisons, *all* of which have $\Delta\Delta E^\ddagger/\Delta\Delta E^\circ > 0$. In all of the cases where the calculations give a confident prediction, *the spin isomer with the greater driving force has the lower barrier*.

The histogram of $\Delta\Delta E^\ddagger/\Delta\Delta E^\circ$ in Figure 3 shows the 42 more confident values in solid purple and the more uncertain ones in hashed gold (five of the latter are off the scale in Figure 3 and not shown). The 42 values form a reasonable distribution, with a median value of $\Delta\Delta E^\ddagger/\Delta\Delta E^\circ$ of 0.8 and a mean (standard deviation) of 0.9 (0.4). The complete dataset has a similar

median (0.7) but a much larger standard deviation about the mean, 1.0 (2.1), presumably due to the uncertainties in the small values of the $\Delta\Delta E^\ddagger/\Delta\Delta E^\circ$ denominator. These values are in modest agreement with the prediction that $\Delta\Delta E^\ddagger/\Delta\Delta E^\circ \approx 0.5$ from equation 4. The distribution is fairly scattered, as expected for a meta-analysis of a diverse set of data with significant uncertainties. Still, the median and mean values indicate that *the barriers are strongly correlated with the driving forces*. In fact, $\Delta E^\ddagger$ may be even more sensitive to ΔE° than predicted by equations 4, as most of the $\Delta\Delta E^\ddagger/\Delta\Delta E^\circ$ values are larger than 0.5.

Of the 59 comparisons, 16 have a lower barrier on the lower-spin surface, $\Delta E^\ddagger(\text{lower spin}) < \Delta E^\ddagger(\text{higher spin})$. These 27% are thus opposite to the hypothesis that higher spin states favor HAT. There is a bias toward lower barriers for high-spin isomers, but not a very strong one.

Singlet states are involved in 15 of the 59 comparisons. In four of these cases (27%), the singlet is calculated to have the lower barrier. Thus, a non-zero spin ground state does not appear to be required for HAT or even a guarantee of a lower barrier for HAT.³⁵

In sum, while there is significant scatter in the data, this meta-analysis indicates that driving force is a primary determinant of HAT barrier. Higher spin states are usually more reactive, but only in ~70% of the cases. Singlet spin states are usually less reactive, but only in ~75% of the cases. It should be noted that some of these comparisons are from studies that focus on the importance of spin states³⁶ or spin density^{36b, 37} and do not discuss driving force. We emphasize that the driving force is not the sole determinant of reactivity, as has been concluded in a number of studies.^{5, 18, 33a, 38} Still, the meta-analysis indicates that the driving force is the largest single determinant of HAT reactivity. We strongly encourage all studies of this kind to start their analyses of differences in HAT barriers in different spin states with a discussion of differences in reaction driving force.

C. Low-spin species are typically more reactive when ΔG° is more favorable

The correlation of barrier with driving force gives predictions and explanations for cases where low-spin states are more reactive. Figure 4 shows the calculated energies for HAT from cyclohexane to $[(\text{N4Py})\text{Fe}(\text{O})]^{2+}$ on three different spin surfaces.²⁵ (A selected portion of this surface, from a later review,²⁴ was shown above as Figure 2.) Overall, the quintet surface has the lowest energy transition state. This $^5\text{TS}_\text{H}$ is 5.9 kcal mol⁻¹ above the reactant cluster on the quintet surface, ^5RC (the values quoted here include solvation energies, from the numbers in square brackets in Figure 4). It should be noted that the singlet state here is an open shell singlet.

On the singlet surface, the computed barrier is 7.5 kcal mol⁻¹ ($E[^1\text{TS}_\text{H}] - E[^1\text{RC}]$), significantly smaller than the 11.9 kcal mol⁻¹ barrier on the triplet surface. Why is the singlet state of $[(\text{N4Py})\text{Fe}(\text{O})]^{2+}$ more reactive than the triplet state? A primary reason appears to be that HAT on the singlet surface is more exoergic. HAT by the singlet is downhill, with $\Delta E = -7.0$ kcal mol⁻¹ while HAT on the triplet surface is uphill, by +2.4 kcal mol⁻¹. The 9.4 greater exoergicity on the singlet surface correlates with a 4.6 kcal mol⁻¹ lower barrier, close to the 4.7 kcal mol⁻¹ predicted by equation 4 ($0.5 \cdot \Delta\Delta E^\circ$).

Comparing the solvated singlet and quintet surfaces, the driving force is slightly less favorable on the higher spin surface (-6.1 vs. -7.0 kcal mol⁻¹), yet the barrier is lower for the higher spin species. While the differences are small, this is not as predicted by equation 4. We discuss this case here to emphasize that eqs 4 will not hold in all cases. Deviations from eqs 4 may be due to differences in reorganization energy for the different spin states, to other contributions to HAT reactivity (see sections IV. A. and IV. B.), or to uncertainties in the computations.

The quintet surface in Figure 4 has the lowest calculated barrier and forms the most stable product, **5I**. The **5I** state is the most stable product because it contains the preferred high-spin sextet ($S = 5/2$) iron(III) hydroxide product, antiferromagnetically coupled to the carbon radical [$^6\text{Fe}^{\text{III}}(\text{OH})+^2\text{R}^\bullet$]. Thus our general prediction is that the quintet state of an $\text{Fe}^{\text{IV}}(\text{O})$ complex will be the most reactive when the $\text{Fe}^{\text{III}}(\text{OH})$ product is high-spin. Of the 39 comparisons involving quintet $\text{Fe}^{\text{IV}}(\text{O})$ states in Table 1, all but four have lower barriers than related triplet or singlet states.

For reactions where the product is much more stable in a low-spin state, the opposite prediction is made: lower spin isomers of the reactant should typically have lower barriers. For instance lower-spin $\text{Fe}^{\text{IV}}(\text{O})$ compounds should be more reactive when the product is low spin ($S = 1/2$) $\text{L}_5\text{Fe}^{\text{III}}(\text{OH})$. A related example of this could be HAT by 4-coordinate C_{3v} symmetric $\text{L}_3\text{Fe}^{\text{IV}}(\text{N})$ species to form $\text{L}_3\text{Fe}^{\text{III}}(\text{NH})$ products; this process should be favored to occur for $S = 0$ nitrido species,³⁹ as the resulting iron(III) imido species in this geometry are known to be $S = 1/2$.⁴⁰ The relationship between spin state and driving force in metal complexes will likely vary from system to system, as factors such as geometry at the metal and d-electron count will modulate the spin selectivity.

IV. A broader view

A. Other contributions to HAT reactivity

This short Essay emphasizes the reaction driving force because this is usually the largest single contributor to the HAT reaction barrier. However, other factors clearly contribute to HAT reactivity, which should be considered when comparing similar reactions with different species. This was emphasized long ago in the organic radical literature and in the valence-bond analyses by Shaik and others.^{6, 18, 27b, 33a, 41} Our more recent Marcus approach has noted the importance of reorganization energies (λ).^{5, 20b, 42} Detailed theories of proton-coupled electron transfer (PCET), of which HAT is one type, include λ as well vibronic overlaps and donor-acceptor motions.⁴³

In addition to these fundamental issues, a number of studies have indicated that steric effects can substantially reduce HAT rate constants.⁴⁴ In an early example, Groves and Nemo suggested in 1983 that steric influences on hydroxylation by iron-oxoporphyrin complexes were due to a stereoelectronic effect on HAT.⁴⁵ This is closely related to the current discussions of σ vs. π mechanisms for H-atom transfer to metal oxo sites.^{37, 46} Very recently, stereochemical effects were suggested to account for the slower HAT reactions of $[\text{Fe}^{\text{IV}}(\text{NTs})(\text{N4Py})]^{2+}$ ($\text{NTs} = \text{tosylimido}^{2-}$) compared to that of $[\text{Fe}^{\text{IV}}(\text{O})(\text{N4Py})]^{2+}$ with C–H bonds; the BDE(NH) and BDE(OH) of the respective product iron(III) species is very similar, and hence so is the driving force.⁴⁷ Stereochemical interactions could, in principle, preclude HAT reactions to occur in systems that have a favorable driving force.

B. Spin density vs. spin states

Spin states are in most cases a clear experimental observable. Molecules in singlet states, for instance, are diamagnetic and have sharp NMR spectra. Most computations, as shown above, have been sorted by spin state.²¹ The section above has analyzed reactions as if they proceed only on one spin surface, the triplet surface for example, for the entire HAT step. This contrasts the idea of TSR, advanced most notably by Shaik.⁴⁸ It should be noted, however, that there is typically rapid interconversion of spin states for transition metal complexes, faster than microseconds for thermodynamically favored processes.⁴⁹ Thus most thermal solution reactions that can access multiple spin states will be under Curtin-Hammett conditions⁵⁰ of rapid equilibration of the reactant and product spin states prior to and subsequent to HAT reaction. Under these conditions, reactions will usually proceed over the

lowest barrier regardless of spin state.^{22, 25} Thus, when multiple spin states are thermally accessible, correlations between spin state and reactivity are not simple.

An alternative perspective is that spin density on the abstracting atom, not spin state, is key to HAT reactivity. Spin density at a particular atom need not correlate with spin state. As a general statement, spin density reflects electronic structure and will influence barrier heights. Spin density difficult to measure experimentally (*cf.*, ⁵¹), and is not usually reported in computational studies. So this suggestion is difficult to address, at least at the moment. Correlating spin density with HAT reactivity for simple organic radicals such as oxyl radicals is complicated by the rough correlation of spin density at O and the O–H bond strength.⁵² Still, it is difficult to reconcile this hypothesis with the HAT reactivity of closed-shell singlets, such as permanganate and α -methylstyrene, that have essentially no spin density on any atom. We return to this issue in the next section.

It has recently been suggested that the key parameter is spin density at the abstracting atom at the transition state.⁵³ Thus a closed-shell singlet reactant could develop spin density at the abstracting atom along the reaction coordinate. In our view, this proposal provides limited insight. HAT is by definition a one-electron process, so the H donor and acceptor each change spin state by $\frac{1}{2}$. Since the transition state is in some ways an interpolation between reactants and products, it is difficult to imagine an HAT reaction in which there isn't some spin density on both reactants at the transition state. There could be more or less spin density at the specific atom that accepts the H, as discussed in the next section. Measuring spin density at a transition state appears to be very difficult, and computing this parameter requires a complete calculation that gives the barrier height, so it is not clear that this perspective has substantial predictive value.

C. Hydrogen atom transfer vs. “proton-coupled electron transfer”

Throughout this essay, “hydrogen atom transfer” (HAT) has been defined as a process that transfers $H^\bullet$ from one reagent $X-H$ to another reagent Y (eq 1). This is the typical usage.

A narrower view is that HAT refers only to reactions in which the proton and electron originate and terminate *in the same bond* (eq 5).⁵⁴ For reactions that fit this narrow definition, the presence of spin density at the abstracting atom may often be a useful heuristic for predicting HAT reactivity. This is frequently the case for reactions of simple p-block radicals, such as the series of oxyl radicals $HO^\bullet$, $RO^\bullet$, $PhO^\bullet$, and $HOO^\bullet$. In such cases, the spin density at Y often parallels the $Y-H$ bond strength, and therefore spin density parallels the HAT driving force and rate constant. One could argue that in these situations the spin density is the fundamental property, leading to the higher $Y-H$ bond strength and reactivity.⁶

The narrow definition, however, excludes many reactions generally called HAT. A variety of HAT reactions – especially those involving metal complexes – involve spatial and/or orbital separation of the e^- and H^+ . The most famous example is from the catalytic cycle of cytochrome P450 (eq 6). The e^- and H^+ are removed from the same C–H bond but transfer to quite separated sites: the proton to the oxo group and the electron to a hole on the porphyrin and thiolate ligands.⁵⁵ Another example is the phenol-phenoxyl self-exchange reaction.⁵⁶ In the extreme case in equation 7, long-range electron transfer from X to Y is concerted with short-range proton transfer from AH to $:B$. Some studies have termed reactions such as equations 6 – 8 “proton-coupled electron transfer” (PCET)^{6,56} and we will use that terminology here for consistency, although ‘PCET’ is increasingly used as a much broader “catch-all” term. One specific example of eq 7 is the self-exchange reaction between iron-biimidazole complexes, the core of which is shown in equation 8.⁵⁷

HAT:

HAT:

(5)

PCET:

PCET:

(6)

(7)

(8)

It should be emphasized that there is a continuum of reactions from “same-bond HAT” to PCET, which adds to the controversy in the role of spin on these reactions. Shaik has referred to these cases as “blended” HAT/PCET” or “variable HAT/PCET mixing.”⁵⁸ Reactions of phenols are a good example, because the SOMO in the product phenoxyl radical is at least as much on the aromatic ring as the oxygen. So does the removed electron “come from” the phenol O–H bond or from the π system? In equation 6, the e^- and H^+ “come from” the same bond but transfer to different places in the product – is this “same-bond HAT” or PCET?

We believe that this continuum between “same-bond HAT” and PCET is at the heart of some of the confusion over the relationship of spin and reactivity. Consider a reaction involving addition of e^- and H^+ ($\text{H}^\bullet$) to an atom X that obeys the octet rule in the product: $\text{X} + \text{H}^\bullet \rightarrow \text{XH}$. The atom X would therefore typically need to have an accessible 7-electron configuration in the reactant or at the transition state, and thus some unpaired spin density. However, if the e^- is transferring to a site that is distant from the proton accepting atom, as

in the ‘PCET’ reactions 6–8, then the proton-accepting atom need not have any unpaired spin density. In this situation, the proton-accepting atom acts only as a base. The electron transfer (ET) portion of the ‘PCET’ process resembles a pure ET step, without any specific spin requirements other than that the overall reaction be spin-allowed.

The self-exchange reaction of ketones and ketyl radicals (eq 9) is an interesting example. These occur with bimolecular rate constants of $\sim 5 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ ($\Delta G^\ddagger = 12 \text{ kcal mol}^{-1}$).⁵⁹ In this process, the singlet ketone is the H-atom acceptor, and its oxygen atom that accepts the H obeys the octet rule. Triplet excited states are not thermally accessible. A purist might argue that this is not a true “same-bond HAT” process, that it occurs only because it is a PCET process with the unpaired electron being primarily on the ketyl carbon. In our view such distinctions are not helpful. These reactions – and many like them – occur readily. The electron and proton find their way to the appropriate sites.

(9)

Many $1e^-/1H^+$ transfer reactions involving transition metals have substantial ‘PCET’ character, and therefore do not require unpaired spin at the abstracting atom, like the ketone in eq 9. We note again that the discussion here is limited to reactions in which the e^- and H^+ transfer in a single concerted step; different issues arise when the transfer occurs via a stepwise ET-PT or PT-ET mechanisms.

Conclusions

A very recent review by Shaik asks and then answers: “‘is there a need to have a radical center at the abstractor in order to abstract a hydrogen atom?’ The answer to this question is, ‘of course not’, but if the abstractor is a closed-shell molecule then in the normal HAT event, this will require a high barrier.”⁶ This appears to contradict the simple kinetic argument in Section II, which demonstrates that open-shell reactants *cannot* be intrinsically more reactive for hydrogen-atom abstraction than closed-shell ones. But the Shaik review is not discussing *intrinsic* barriers in that quote, but rather absolute barriers. It states soon after that: “the BDE_{OH} [bond dissociation energy] quantity for the closed-shell abstractors already incorporates the cost of decoupling the bonds of the closed-shell abstractors and preparing them for abstracting an H atom.” In other words, the difference between open and closed-shell reactants is manifest in the bond strength and therefore in the driving force for HAT. This difference in driving force then affects the transition state energy. Thus that review and this essay agree in important ways, despite the apparently contradictory language. The indirect effects of spin appear to be more important for the very narrowly defined “same bond” HAT processes. In “same bond” HAT, closed-shell abstractors have a “cost” to “prepare them for abstracting an H atom,” in Shaik’s VB language. In contrast, in ‘PCET’ reactions where the e^- and H^+ are well separated, there is no such cost.

The common intuition that HAT is facilitated by the presence of unpaired spin at the abstracting atom derives from organic radical chemistry. For main-group compounds, an open-shell reactant is usually needed in order to have sufficient thermodynamic driving force for HAT. However, unpaired spin is not required for HAT even in organic chemistry, as shown by Rüchardt’s reverse radical disproportionation reactions and the ketone reaction 9.^{10, 59} For HAT reactions involving transition metal ions, where there is often substantial

separation of the e^- and the H^+ , spin states and spin density are more distantly connected to reactivity.

This essay shows, through simple kinetic argument (Section II) and a meta-analysis of computational studies (Section III) that HAT reactivity is best understood starting from the driving force for the HAT step. Barrier heights sometimes parallel spin multiplicities, but almost always correlate with reaction energy. The effects of spin state on HAT are indirect, mostly through the reaction driving force.

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Appendix A

Table 1

DFT-calculated activation and reaction free energy changes for HAT reactions of Fe or Mn complexes with organic substrates in various spin states. Energies are given in kcal mol^{−1}. hs and ls refer to the higher and lower spin states, respectively.

Reactants	Spin states/[a] (mechanism)[b]	ΔE (hs)	ΔE (ls)	ΔΔE (hs-ls)	ΔE* (hs)	ΔE* (ls)	ΔΔE* (hs-ls)	ΔΔE / ΔΔE*	Ref.
[Fe ^{III} O] ⁺ + C ₂ H ₆ [c]	quartet/sextet	23.2	16.2	7.0	−0.1	−3.5	3.4	2.1	60
[Fe ^{III} O] ⁺ + C ₂ H ₆ [d]	quartet/sextet	21.2	14.5	6.7	6.3	−2.1	8.4	0.8	60
[(TMG ₃ tren)Fe ^{IV} O] ²⁺ + C ₆ H ₈ [de]	triplet(π)/quintet(σ)	15.6	12.3	3.3	−12.3	−22.1	9.8	0.3	36a
[(N4Py)Fe ^{IV} O] ²⁺ + C ₆ H ₈ [df]	quintet(σ)/triplet(π)	−1.4	13	−14.4	−25.8	−15.5	−10.3	1.4	36a,61
[(TMC)(MeCN)Fe ^{IV} O] ²⁺ + C ₆ H ₈ [dg]	triplet(π)/quintet(σ)[h]	7.1	18.8	−11.7	−15.9	−8.1	−7.8	1.5	36a
(Tp)(OBz)Fe ^{IV} O + C ₆ H ₈ [ijk]	triplet(π)/quintet(σ)	6.3	12.5	−6.2	−28.7	−20.1	−8.6	0.7	36a
[(N4Py)Fe ^{IV} O] ²⁺ + C ₆ H ₁₂ [df]	quintet(σ)/triplet(π)	5.9	11.9	−6.0	−6.1	2.4	−8.5	0.7	25
[(N4Py)Fe ^{IV} O] ²⁺ + toluene[df]	singlet/triplet(π)	11.9	7.5	4.4	2.4	−7.0	9.4	0.5	25
	singlet/quintet(σ)	5.9	7.5	−1.6	−6.1	−7.0	0.9	−1.8	25
	quintet(σ)/triplet(π)	3.7	11.4	−7.7	−11.8	−4.7	−7.1	1.1	25
	singlet/triplet(π)	11.4	13.8	−2.4	−4.7	−10.3	5.6	−0.4	25
[(Bn-TPEN)Fe ^{IV} O] ²⁺ + C ₆ H ₁₂ [dl]	singlet/quintet[h]	3.7	13.8	−10.1	−11.8	−10.3	−1.5	6.7	25
	quintet(σ)/triplet(π)	7.1	12.5	−5.4	−5.6	0.9	−6.5	0.8	25
	singlet/triplet(π)	12.5	9.4	3.1	0.9	−8.2	9.1	0.3	25
[(TMC)(MeCN)Fe ^{IV} O] ²⁺ + C ₆ H ₁₂ [dg]	singlet/quintet(σ)	7.1	9.4	−2.3	−5.6	−8.2	2.6	−0.9	25
	quintet(σ)/triplet(π)	10.8	23.2	−12.4	−0.4	9.4	−9.8	1.3	25
	singlet/triplet(π)	23.2	17.6	5.6	9.4	1.1	8.3	0.7	25
	singlet/quintet(σ)	10.8	17.6	−6.8	−0.4	1.1	−1.5	4.5	25
[(TMC)(OTf)Fe ^{IV} O] ⁺ + C ₆ H ₁₂ [dg]	quintet(σ)/triplet(π)	9.8	22.8	−13.0	−0.7	9.1	−9.8	1.3	25
	singlet/triplet(π)	22.8	17.0	5.8	9.1	−0.2	9.3	0.6	25
	singlet/quintet(σ)	9.8	17.0	−7.2	−0.7	−0.2	−0.5	14.4	25
	quintet(σ)/triplet(π)	7.8	23.2	−15.4	−2.4	11.4	−13.8	1.12	61
[(N4Py)Fe ^{IV} O](ClO ₄) ₂ + C ₆ H ₈ [df]	quintet(σ)/triplet(π)	2.8	14.4	−11.6	−28.1	−14.0	−14.1	0.82	61
	quintet(π)/triplet(σ)	13.1	20.2	−7.1	−28.1	−14.0	−14.1	0.5	61
	quintet(π)/triplet(π)	13.1	14.1	−1.3	−28.1	−14.0	−14.1	0.09	61
	quintet(σ)/triplet(σ)	2.8	20.2	−17.4	−28.1	−14.0	−14.1	1.23	61
[(TMC)(MeCN)Fe ^{IV} O] ²⁺ + PhC ₂ H ₅ [dg]	quintet(σ)/triplet(π)	11.2	24.7	−13.5	−4.9	4.3	−9.2	1.47	62
[(TBC)(MeCN)Fe ^{IV} O] ²⁺ + PhC ₂ H ₅ [d,v]	quintet(σ)/triplet(π)	8.7	25.0	−16.3	−7.5	3.3	−10.8	1.51	62

Reactants	Spin states/[a] (mechanism)[b]	ΔE (hs)	ΔE (ls)	$\Delta \Delta E$ (hs-ls)	ΔE^* (hs)	ΔE^* (ls)	$\Delta \Delta E^*$ (hs-ls)	$\Delta \Delta E$ / $\Delta \Delta E^*$	Ref.
$[(\text{NH}_3)_5 \text{Fe}^{\text{IV}}\text{O}]^{2+} + \text{C}_2\text{H}_6[d]$	quintet(σ)/triplet(σ)	9.7	20.3	-10.6	-1.3	14.1	-15.4	0.7	37
	quintet(π)/triplet(π)	17.1	16.3	0.8	6.9	6.0	0.9	0.9	37
	quintet(σ)/triplet(π)	9.7	16.3	-6.6	-1.3	6.0	-7.3	0.9	37
	quintet(π)/triplet(σ)	17.1	20.3	-3.2	6.9	14.1	-7.2	0.4	37
	triplet(π)/quintet(π)[m]	19.7	14.4	5.3	18	5.3	12.7	0.4	37
	triplet(π)/quintet(σ)[m]	3.1	14.4	-11.3	-11.4	5.3	-16.7	0.7	37
$[(\text{OH})_{\text{axial}}(\text{NH}_3)_4 \text{Fe}^{\text{IV}}\text{O}]^+ + \text{C}_2\text{H}_6[d]$	triplet(π)/quintet(π)	20.4	20.5	-0.1	7.2	10.6	-3.4	0.0	37
	triplet(π)/quintet(σ)	16.3	20.5	-4.2	3.5	10.6	-7.1	0.6	37
	triplet(π)/quintet(σ)[m]	9.9	24.5	-14.6	-7.7	11.5	-19.2	0.8	37
$[(\text{OH})_2(\text{equatorial})(\text{NH}_3)_3 \text{Fe}^{\text{IV}}\text{O}]^+ + \text{C}_2\text{H}_6[d]$	triplet(π)/quintet(π)[h]	19.3	24.5	-5.2	9.7	13.8	-4.1	1.3	37
	triplet(π)/quintet(σ)[h]	11.8	24.5	-12.7	-0.9	13.8	-14.7	0.9	37
	triplet(π)/quintet(π)[m]	23.9	32.1	-8.2	15.7	23.2	-7.5	1.1	37
	triplet(π)/quintet(σ)[m]	4.1	32.1	-28.0	-12.8	23.2	-36.0	0.8	37
$[(\text{TMC})(\text{OTf})\text{Fe}^{\text{IV}}\text{O}]^+ + \text{C}_6\text{H}_8[d,g]$	quintet(σ)/triplet(π)	4.8	15.8	-11.0	-21.5	-11.3	-10.2	1.1	34
$(\text{Hp}^{\bullet+})(\text{OH})\text{Fe}^{\text{IV}}\text{O} + \text{C}_3\text{H}_6[n]$	doublet/quartet	5.7	2.9	2.9	-16.4	-17.5	1.1	2.6	33a
$\text{Cpd I}(\text{C}_6\text{P}) + \text{C}_3\text{H}_6[o]$	doublet/quartet	18.4	17.8	0.6	2.6	1.7	0.9	0.7	33a
$(\text{tHp})(\text{Cl})\text{Mn}^{\text{VO}} + \text{toluene}[n]$	quintet/triplet	3.6	2.7	0.9	-10.9	-4.2	-6.7	-0.4	9
$[(\text{tHp})(\text{H}_2\text{O})\text{Mn}^{\text{VO}}]^+ + \text{toluene}[d,n]$	quintet/triplet	2.2	0.4	1.8	-8.6	-5.7	-2.9	-0.6	9
$(\text{tHp})(\text{OH})\text{Mn}^{\text{VO}} + \text{toluene}[d,n]$	quintet/triplet	-0.7	4.3	-5.0	-17.5	-4.2	-13.3	0.4	9
$[(\text{tHp})(\text{O})\text{Mn}^{\text{VO}}]^- + \text{toluene}[d,n]$	quintet/triplet	2.0	8.0	-6.0	-19.4	-6.3	-13.1	0.5	9
$(\text{tpp})(\text{Cl})\text{Mn}^{\text{VO}} + \text{DHP}[d,p,q]$	quintet/triplet	1.8	0.9	0.9	-15.1	-9.7	-5.4	-0.2	63
$(\text{C}_2)\text{Mn}^{\text{VO}} + \text{DHA}[r,s,t]$	triplet B[u]/singlet	6.1	22.8	-16.7	-13.9	14.9	-28.8	0.6	36b
	triplet A[u]/singlet	15.7	22.8	-7.1	0.3	14.9	-14.6	0.5	36b
$[(\text{C}_2)(\text{F})\text{Mn}^{\text{VO}}]^- + \text{DHA}[r,s,t]$	triplet B[u]/singlet	2.5	14.6	-12.1	-23.0	-4.3	-18.7	0.6	36b
	triplet A[u]/singlet	4.9	14.6	-9.7	-14.8	-4.3	-10.5	0.9	36b
$[(\text{C}_2)(\text{CN})\text{Mn}^{\text{VO}}]^- + \text{DHA}$	triplet B[u]/singlet	-0.6	10.7	-11.3	-23.9	-5.9	-18.0	0.6	36b
	triplet A[u]/singlet	18.4	10.7	7.7	-8.1	-5.9	-2.2	-3.5	36b
$(\text{tHp})\text{Fe}^{\text{IV}}\text{O} + \text{CH}_4[n,t]$	quintet(σ)/triplet(π)	11.7	27.2	-15.5	3.7	24.2	-20.5	0.76	64
	quintet(σ)/triplet(σ)	11.7	23.0	-11.3	3.7	17.3	-13.6	0.83	64
$[(\text{tHp})(\text{SH})\text{Fe}^{\text{IV}}\text{O}]^- + \text{CH}_4[n,t]$	quintet(σ)/triplet(π)	22.8	22.9	-0.1	16.2	17.0	-0.8	0.13	64
	quintet(π)/triplet(π)	25.0	22.9	2.1	19.3	17.0	2.3	0.91	64

[a] Listed as [higher energy spin state]/[lower energy spin state] for the reactants.

[b] A π mechanism denotes transfer of a β electron from the nucleophile into a π^* orbital of the metal oxo reagent. A σ mechanism denotes transfer of a β electron from the nucleophile into a σ^* orbital of the metal oxo reagent.

[c] Calculated gas phase energies.

[d] Calculated energies in acetonitrile solvent.

[e] TMG3tren = 1,1,1-tris{2-[N2-(1,1,3,3-tetramethylguanidino)]ethyl}amine.

[f] N4Py = N-bis(2-pyridylmethyl)-N-(bis-2-pyridylmethyl)amine.

[g] TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane.

[h] The reactant energies are calculated to be equivalent in both spin states.

[i] Tp = 3,5-diphenylpyrazolyl)hydroborate.

[j] OBz = benzylformate.

[k] Calculated energies in benzene solvent.

- [l] Bn-TPEN = N-benzyl-N,N',N'-tris(2-pyridylmethyl)ethane-1,2-diamine.
- [m] Energies calculated with coupled-cluster theory.
- [n] tHp = tetrahydrogenporphyrin.
- [o] Cpd I(CcP) = compound I model for cytochrome c peroxidase.
- [p] tpp = tetraphenylporphyrin.
- [q] DHP = 9,10-dihydrophenanthroline.
- [r] Cz = corrolazinato3-.
- [s] DHA = 9,10-dihydroanthracene.
- [t] Calculated energies with chlorobenzene solvent.
- [u] Two low-lying triplet states are present in this system: in triplet A, the unpaired electrons are located in a MnO π^* orbital and a ligand a1u orbital, while in triplet B, the unpaired electrons are located in a MnO π^* orbital and the Mn δ orbital.
- [v] TBC = 1,4,8,11-tetrabenzyl-1,4,8,11-tetraazacyclotetradecane.

Figure 1. Schematic free energy surface for the HAT reaction of two closed-shell species $X: + H-Y \rightarrow X-H^\bullet + Y^\bullet$ (eq 2), indicating the free energy barriers ($\Delta G^\ddagger$) for the forward and reverse reactions and the driving force (ΔG°_2).

Figure 2.

From Figure 1b of reference ²⁴. "Gas-phase energy profiles [kcal mol⁻¹] calculated with B3LYP." N4Py = N,N-bis(2-pyridylmethyl)-N-(bis-2-pyridylmethyl)amine, R-H = C₆H₁₂. Reprinted by permission from Macmillan Publishers Ltd: [Nature Chemistry] (ref. ²⁴), copyright (2011).

Figure 3.

Histogram of $\Delta\Delta E^\ddagger/\Delta\Delta E^\circ$ values from Appendix A. The solid purple bars are for cases with confident predictions, while the gold hashed bars have $|\Delta\Delta E^\ddagger|$ and/or $|\Delta\Delta E^\circ| < 2.5$ kcal mol⁻¹. Five gold cases are not shown, at $\Delta\Delta E^\ddagger/\Delta\Delta E^\circ = +14, 6.7, 4.5, -1.8$ and -3.5 .

Figure 4.

Figure 2 from reference ²⁵. “Energy profile for the reaction of $2S+1K_{N4Py}$ ($S = 0, 1, 2$) with cyclohexane (C_6H_{12}). Relative energies are indicated in the order: B2//B1 (B2//B1 + ZPE) [B2//B1 + ZPE + E_{solv}].” Abbreviations: K = $[(N4Py)Fe(O)]^{2+}$, CH = cyclohexane, RC = reactant cluster (the precursor to the H-atom transfer), TS_H = the HAT transition state, and I = the immediate product of HAT, which is one intermediate along the complete reaction pathway. Energies quoted in the text are differences between RC, TS_H , and I (for a particular spin state), using values that correspond to B2//B1 + ZPE + E_{solv} (in brackets). Reprinted with permission from ²⁵. Copyright (2006) American Chemical Society.