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Hydrogen Atom Abstraction by Metal−Oxo Complexes: Understanding the Analogy with Organic Radical Reactions

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Introduction

Hydrogen atom transfer (eq 1) is one of the most fundamental and most common chemical reactions, from the

$$X + H{-}Y \rightarrow X{-}H + Y \qquad (1)$$

industrial plant to the chemical lab to the enzyme active site. Abstraction of a hydrogen atom is a key step in most hydrocarbon oxidations, both in complete combustion (humanity's largest scale chemical reaction) and in many industrial partial oxidation processes.[1] The industrial processes include both homogeneous and heterogeneous oxidations, for instance *p*-xylene to terephthalic acid and propylene to acrylonitrile, and total more than 10^{10} lb/yr of U.S. production alone.[2] Hydrogen atom abstraction is playing an increasing role in organic synthesis, for instance the use of manganese acetate for oxidative cyclizations.[3] There are also a variety of biochemical processes that appear to involve one or more H-atom transfer steps, including the antioxidant vitamin E[4] and the anticancer drug bleomycin and other DNA cleaving protocols.[5] H• transfer has been implicated in the catalytic cycles of a variety of metalloenzymes, including the oxidation of fatty acids by lipoxygenases,[6] the biosynthesis of dopamine,[7] and the processing of various metabolites and xenobiotics by cytochrome P450 enzymes.[8]

The abstracting agent in H-atom transfer reactions (X in eq 1) is often a reactive main group radical, a species with at least one unpaired electron spin. For instance, the commercial oxidation of cyclohexane to adipic acid involves alkoxyl and alkylperoxyl radicals.[9] In other cases, however, the abstracting agent is a coordination complex containing a transition metal ion (eq 2). The presence or

$$L_nM{-}X + H{-}Y \rightarrow L_nM{-}X{-}H + Y \qquad (2)$$

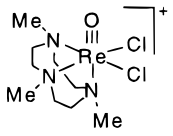
absence of unpaired electrons in such complexes does not correlate with reactivity and therefore cannot be used to understand H• transfer. So instead of looking at the spin state of the abstracting agent as a whole, it has been assumed that the necessary requirement is radical character at the ligand that accepts the H (X in eq 2). This has been used to rationalize, for instance, the H-atom abstracting ability of the iron−oxo active site of cytochrome P450 enzymes: "The transfer of unpaired electron density to the oxygen, which determines its propensity to enter into radical reactions, ..." [10] From this perspective, nature accomplishes H-atom abstraction by creating an oxygen radical in a controlled fashion within an active site. The same idea can be found in discussions of heterogeneous oxidation reactions, where surface $O^{\bullet-}$ and other radicals have been suggested as abstracting agents.[11]

On the basis of this intuition, we set out to make, characterize, and study metal−oxo complexes with unpaired spin density at oxygen. This Account describes our progression from thinking about radicals and spin density to an approach based on the thermochemistry of the hydrogen atom transfer step. The spin-density intuition was based on an analogy with organic radical chemistry, but as described below, a better analogy is based on bond strengths. This approach provides both new qualitative insight and quantitative predictions.

Attempted Generation of Metal−Oxo "π^* Radicals"

Metal complexes with a terminal oxo ligand typically have d^0, d^1, or d^2 electronic configurations.[12] Only the d^1 compounds have an unpaired spin, but it is principally localized in a metal orbital orthogonal to the metal−oxo bond. Removal of an electron from a d^0 complex could generate an "M═O•" species, but this would be a very high energy process and has yet to be documented for a solution species. Our approach to isolate complexes with some spin density at oxygen was the population of a metal−oxygen π-antibonding (π^*) orbital, by adding an electron to d^0 or d^2 oxo compounds. Such M═O π^* orbitals are partially occupied in a number of stable ruthenium− and osmium−oxo complexes[13] and are suggested to be the location of the unpaired spins in the ferryl active site of cytochrome P450 and peroxidases.[8]

The d^2 cation $[(Me_3tacn)Re(O)Cl_2]^+$



was prepared by Becky Conry in 1988[14] with the goal of

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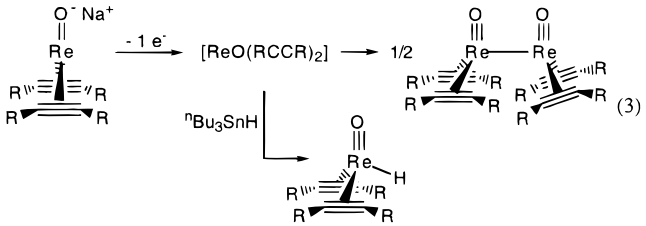
adding an electron into its Re═O π^* LUMO, facilitated by the positive charge. It is reduced electrochemically at −1.1 V vs $CpFe^{0/+}$ in THF, but no products could be isolated from chemical reductions. We had no success trapping a reduced intermediate by hydrogen atom transfer. Similarly discouraging results were obtained in other systems, including reduction of the related d^0 complexes $[(Me_3\text{-tacn})Re(O)_3]^+$ and $[(tacn)Re(O)_3]^+$.[15]

At about the same time, we were studying an unusual rhenium−oxo−bis(alkyne) anion whose doubly-occupied HOMO has significant Re═O π^* character.[16] One-electron oxidation of the anion gives the odd-electron Re(II) species $Re(O)(RC{\equiv}CR)_2$ which exhibits radical reactivity: it dimerizes to a metal−metal-bonded complex, couples with carbon radicals, and, in low yield, abstracts the weakly bound hydrogen atom from $^nBu_3SnH$ (eq 3).[17] But these



(3)

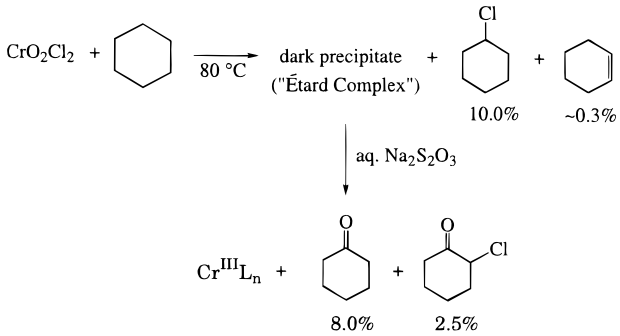
reactions all occur at the rhenium center to give Re−Re, Re−C, or Re−H bonds, not at the oxo ligand.[18] This dichotomy between the $Re^{II}(O)$ radical and the P450 ferryl group is likely due to the rhenium complex being a reducing agent while the ferryl is an oxidant. Addition of H• to the metal is a formal oxidation of the metal center, while H• addition at the oxo ligand is a reduction of M. The reacting rhenium compounds above are reductants, not oxidants. This led us to discard the idea of making an oxidant by reduction. We therefore moved to more oxidizing systems, and we began to think about reaction thermodynamics as a predictor of reactivity.

C−H Bond Oxidation by CrO_2Cl_2[19,20]

The oxidation of hydrocarbons by chromyl chloride, CrO_2Cl_2 (*e.g.*, Scheme 1), is known as the Étard reaction and dates from the 19th century. In the 1960s, Wiberg and co-workers argued convincingly for radical intermediates though carbocation and concerted pathways have been more recently advanced.[21] Wiberg suggested that Cr^{VI} complexes abstract hydrogen atoms from substrates but also considered radical chain paths in which another oxidant performed the initial abstraction. This latter scenario seemed to us consistent with a 1951 report that "methylcyclohexane shows little tendency to react with chromyl chloride .... However the addition of less than 1% of an olefin initiated a moderately rapid reaction."[22] We imagined a chain mechanism with a Cr^V intermediate, possessing some radical character at oxygen, in line with the oxygen radical paradigm sketched above. CrO_2Cl_2 itself is d^0 and has no unpaired electrons.

Jerry Cook found, however, that the 1951 report is incorrect: alkane oxidation is unaffected by the presence of an alkene (which is rapidly consumed by reaction with

Scheme 1. Reaction of CrO_2Cl_2 with Cyclohexane

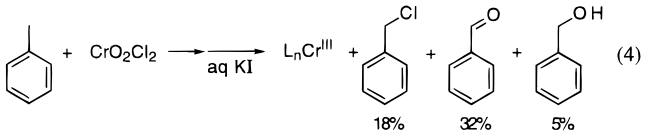


Yields are per mole of CrO_2Cl_2

CrO_2Cl_2).[22b] Discarding our first hypothesis, we set out to do a full mechanistic study of cyclohexane oxidation,[19] which was followed by studies of isobutane, cyclooctane, and toluene.[20] All reactions were done anaerobically and in the dark, with vacuum line techniques, and used highly purified reagents.

Following the kinetics was the first technical challenge because of rapid precipitation of the products. Jerry decided to monitor the reactions using the optical absorbance of volatile red CrO_2Cl_2 in the gas phase above the reaction solution, which required construction of special cells and cell holders.[19,20] Good kinetic data were obtained: reactions in the presence of excess substrate follow first-order kinetics to typically ≥4 half-lives. The same apparatus has been used in preliminary studies of gas-phase reactions of CrO_2Cl_2 with hydrocarbons, in the absence of a liquid phase. These reactions proceed to similar products and with similar rate constants as in solution. Such similarity of gas- and liquid-phase reactions is common for hydrogen atom transfer but rules out mechanisms with significant charge accumulation in the transition state.

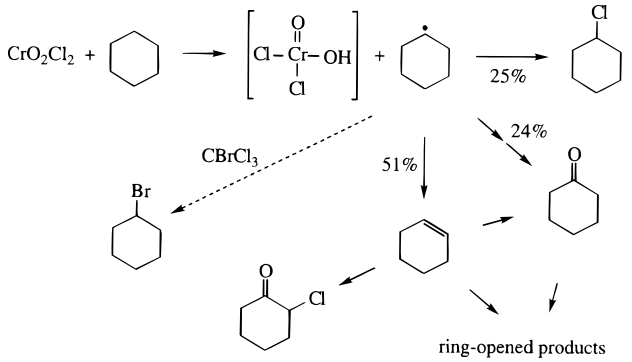
Providing an accounting of the mass balance or stoichiometry of these reactions was also a challenge. The chromium products (Étard complexes) are nonstoichiometric materials with average chromium oxidation states between 3 and 4 by iodometric titration. The observed organic products from cyclohexane (Scheme 1) account for only 26% of the chromium oxidative equivalents consumed. The products from toluene oxidation (the classic Étard reaction) provide 84% mass balance (eq 4).



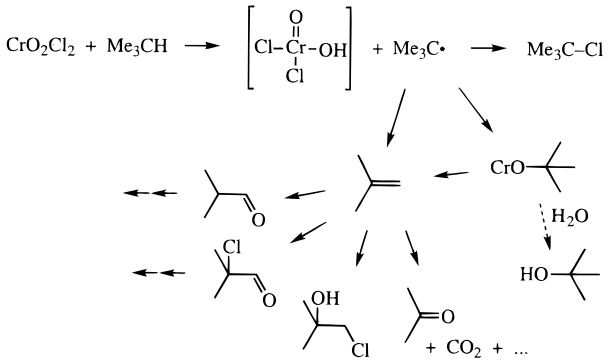
(4)

Incomplete mass balance is common in oxidation reactions because of the variety of products formed and because extensive oxidation of a small amount of material can consume a large amount of oxidant. In the CrO_2Cl_2 reactions, various evidence indicates that the unobserved product(s) are carboxylates such as adipate $[^-O_2C(CH_2)_4CO_2^-]$ from cyclohexane and benzoate from toluene. These are difficult to liberate from the substitution-inert Cr^{III} products.

Scheme 2. Mechanism of Chromyl Chloride Oxidation of Cyclohexane



Scheme 3. Oxidation of Isobutane by CrO_2Cl_2

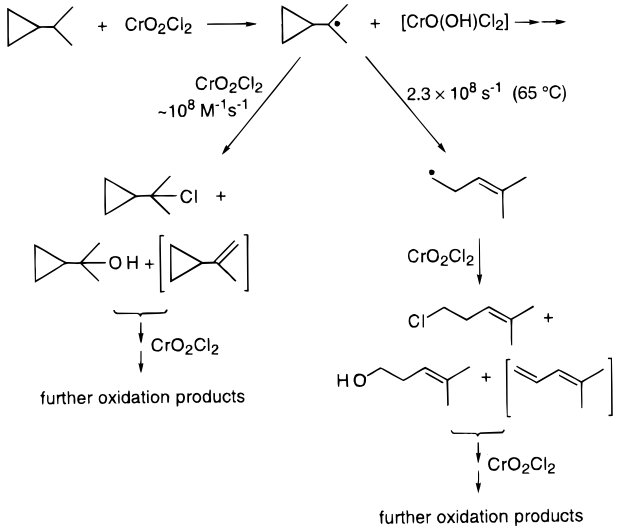


The data show that, for each of the four substrates, the rate-limiting step is simple bimolecular attack of CrO_2Cl_2 on the hydrocarbon. This seemingly trivial conclusion opened the door to an understanding of the reactions: the key reactive species is the material we put in the flask—CrO_2Cl_2—and not a fleeting intermediate whose properties would be difficult to probe. This contrasts with the more common and perhaps more relevant approach of using the metal complex as a catalyst or catalyst precursor (as nature does), with the active oxidant generated *in situ* by the terminal oxidant (oxygen, peroxides, iodosyl benzene, hypochlorite, etc.).

The initial reaction of CrO_2Cl_2 + RH proceeds by hydrogen atom transfer to give the carbon radical (*cf.*, Schemes 2 and 3).[19,20] Cyclohexyl radicals were trapped by adding $CBrCl_3$ to cyclohexane reactions,[23] in experiments that had to be done with care to avoid the independent radical chain oxidation of cyclohexane by $CBrCl_3$. The dependence of bromocyclohexane yield on initial CrO_2Cl_2 concentration showed[19] that C_6H_{11}• is predominantly formed and consumed by CrO_2Cl_2. Trapping of C_6H_{11}• by CrO_2Cl_2 is very rapid ($k_2 \cong 3 \times 10^9$ M^{-1} s^{-1}).[24] This provides a cautionary note to the use of radical traps as a mechanistic test when the oxidizing metal complex is itself a rapid trap—in this case, CCl_4 would not have been a fast enough trap.

The reaction of R• with CrO_2Cl_2 can occur by Cl• transfer to give R−Cl, by transfer of an α-hydrogen from R• to give an alkene, or by addition of R• to an oxo group to give a chromium(V) alkoxide (a precursor to alcohol, aldehyde, carboxylate, and possibly alkene products). For the cyclohexyl radical, all three trapping pathways occur at roughly equal rates because they each occur with essentially no barrier ($k \sim 10^9$ M^{-1} s^{-1}). The overall mechanism (Scheme 2) accounts for 88(10)% of the chromium oxidizing equivalents consumed, using independent data from cyclohexene oxidations under the same conditions. In the toluene reaction, the benzyl radical is trapped only by C−O or C−Cl bond formation (eq 4) because there is no β-hydrogen. Isobutane oxidation gives the *tert*-butyl radical by initial abstraction from the weak tertiary C−H bond. ^{t}Bu• is then oxidized by CrO_2Cl_2 primarily to isobutylene, plus some ^{t}BuCl and ^{t}BuOH. The alkenes formed in these reactions are rapidly oxidized by CrO_2Cl_2, consistent with previous studies (including Sharpless' pioneering suggestion of organometallic intermediates in olefin oxidations[25]) indicating that epoxides and chlorohydrins are the initial products.[19,21,25]

Scheme 4. Oxidation of Isopropylcyclopropane by CrO_2Cl_2



CrO_2Cl_2 oxidation of isopropylcyclopropane (Scheme 4)[26] proceeds by H-atom abstraction to give the dimethyl cyclopropyl carbinyl radical, which ring-opens at 2.3×10^8 s^{-1} at 65 °C.[27] This reaction yields a myriad of products because CrO_2Cl_2 reacts by multiple paths with both the alkene and radical functionalities. Kun Wang was able to identify both unrearranged and ring-opened oxidation products, consistent with CrO_2Cl_2 trapping the tertiary radical at $10^{8\pm1}$ M^{-1} s^{-1}. Quantitative analysis was not possible due to the number of products and pathways.

The mechanism of CrO_2Cl_2 oxidations is quite similar to that proposed for cytochrome P450 oxidations of C−H bonds, the "oxygen rebound" path of hydrogen atom abstraction followed by rapid trapping of the carbon radical.[8] This had been previously proposed for chromium(VI) oxidations by Wiberg[21a−c] and by Stephenson[28] to account for the predominant retention of stereochemistry on oxidation of chiral tertiary C−H bonds. It should be noted that recent studies with very rapid radical clock substrates have questioned the oxygen rebound mechanism, at least for enzymatic reactions.[29]

The rate of the initial hydrogen atom transfer step is equal to the rate of disappearance of CrO_2Cl_2 times the

Table 1. Rates, Isotope Effects, and Activation Parameters for the Initial Step of Reactions of CrO_2Cl_2 with Cyclohexane, Cyclooctane, Isobutane, and Toluene[19,20]

substrate	k(340 K) (M^{-1} s^{-1})[a]	k_H/k_D	$\Delta H^‡$ (kcal/mol)	$\Delta S^‡$ [a] (eu)	$\Delta G^‡$ [a] (kcal/mol)	D(C−H)[30] (kcal/mol)
C_6H_{12}	1.38×10^{-7}	2.2(2)[b]	26.6(8)	−12(2)	30.7(7)	99.3
C_8H_{16}	1.86×10^{-5}		19.4(2)	−22.8(5)	27.4(3)	95.7
$(CH_3)_3CH$	2.33×10^{-5}	2.3(3)[c]	20.4(8)	−20(5)	27.2(7)	96.5
$C_6H_5CH_3$	7.03×10^{-4}	8.0(8)[d]	15.5(4)	−28(1)	24.9(5)	89.9

[a] Values per reactive hydrogen at 340 K. [b] $k_{C_6H_{12}}/k_{C_6D_{12}}$ at 75.0 °C. [c] k_{Me_3CH}/k_{Me_3CD} at 59.9 °C. [d] $k_{C_7H_8}/k_{C_7D_8}$ at 50.0 °C.

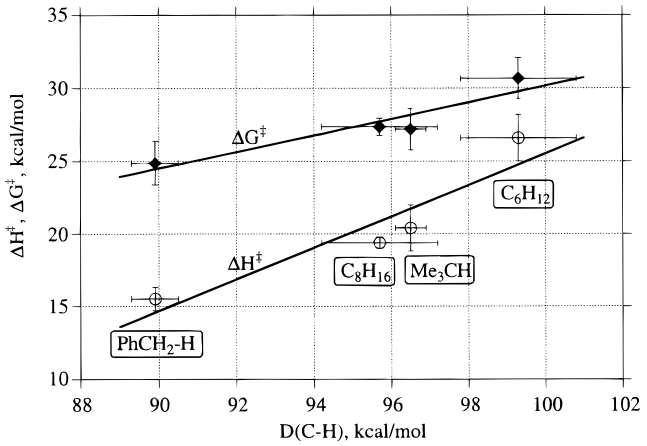


FIGURE 1. Correlations of $\Delta H^‡$ and $\Delta G^‡$ with C−H bond strength for CrO_2Cl_2 oxidations of cyclohexane, isobutane, cyclooctane, and toluene. Adapted from ref 20.

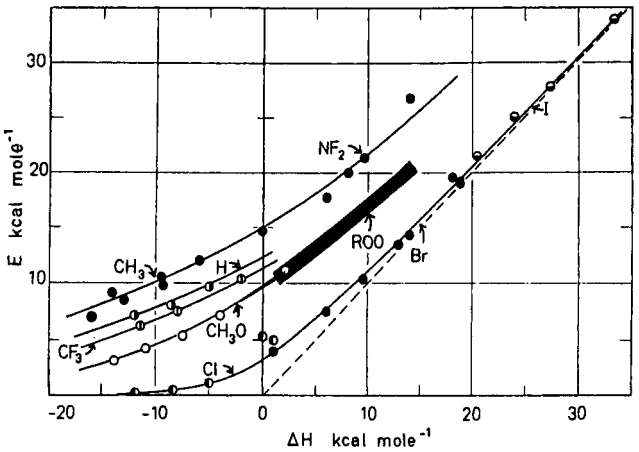


FIGURE 2. Dependence of activation energy, E, on heat of reaction, ΔH, for various radicals. Reprinted from ref 33. Copyright 1968 American Chemical Society.

number of CrO_2Cl_2 consumed per R• formed. The derived $\Delta H^‡$ and $\Delta G^‡$ for this step correlate well with the strengths of the C−H bonds being cleaved (Table 1, Figure 1).[30] This is equivalent to a correlation with $\Delta H°$, which is the difference between the strengths of the C−H bond being cleaved and the O−H bond being formed. Adding 1 kcal/mol to the C−H bond strength increases $\Delta H^‡$ and $\Delta G^‡$ by roughly 1.1 and 0.6 kcal/mol, respectively. This correlation is a powerful piece of mechanistic data. It would not hold if carbocations were formed because toluene and isobutane would form much more stable intermediates than the two cycloalkanes. [2+2] addition of a C−H bond across an M=O bond to give M(R)(OH) would be sensitive to the steric properties of the alkyl ligand and to the strength of the metal−carbon bond, as found for related reactions of M=NR complexes.[31] These show a correlation *opposite* to that observed here, with stronger C−H bonds more easily activated and no activation of tertiary C−H bonds.

The correlation of rate constants and activation parameters with C−H bond strengths ($\Delta H°$) is typical of main group hydrogen atom transfer reactions, as first enunciated by Evans and Polanyi in the 1930s.[32] This is an empirical extrathermodynamic relationship that does not apply to chemical reactions in general (or even to other types of radical reactions). But the correlation holds quite well for H-atom transfer over a wide range of driving force when comparing similar radicals with similar substrates, for instance for oxygen radicals attacking C−H bonds (Figure 2[33]). The reactivity of CrO_2Cl_2 is reminiscent of oxygen radicals, even though it is not a radical. Parallel studies with permanganate were required to understand this reactivity.

C−H Bond Oxidation by Permanganate, MnO_4^- [34,35]

Permanganate oxidations of alkyl aromatic compounds have been studied for over a century and appear in most introductory organic chemistry texts. Yet the mechanism(s) of these reactions are not well established, with proposals including H• abstraction, hydride abstraction, and [2+2] pathways.[36] An early review stated that "Ions derived from every valence state of manganese from VII to III, as well as the hydroxyl radical and other oxygenated species (*e.g.*, O^- and HO_2) have been proposed as the active entities responsible for oxidation by permanganate." [36a]

Our efforts[34,35] have focused on oxidations in aprotic organic media. $^nBu_4NMnO_4$ has sufficient solubility in toluene (~0.3 mM) for mechanistic studies but is reported to be explosive.[37] Kim Gardner found that $^nBu_4NMnO_4$ decays in toluene over 1 week at ambient temperatures to give colloidal MnO_2. The dominant organic product is benzoate which is bound to the surface of the colloid and must be liberated by aqueous reduction. The benzoate and benzaldehyde in the aqueous layer account for 62% of the MnO_4^- oxidative equivalents used. The unobserved products may be in the organic layer or formed on oxidation of benzoate or the $^nBu_4N^+$ counterion. Product analyses were hampered by the small quantities of material, due to the low solubility of $^nBu_4NMnO_4$. Similar results were obtained on oxidation of ethylbenzene, diphenylmethane, triphenylmethane, dihydroanthracene,

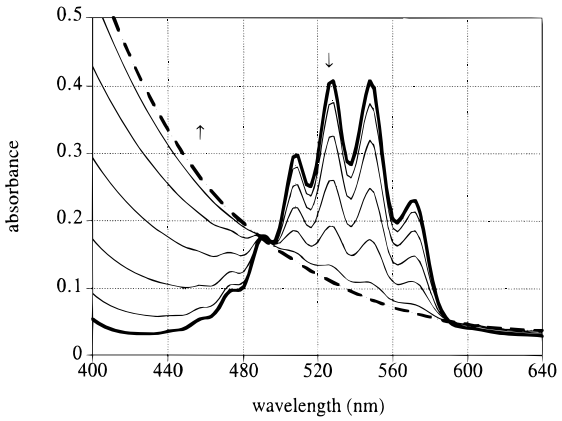


FIGURE 3. Overlay of UV/vis spectra showing the conversion of $^{n}Bu_4NMnO_4$ to MnO_2 in toluene. Reprinted from ref 35. Copyright 1997 American Chemical Society.

or xanthene, which were performed in toluene solvent.

The decay of $^{n}Bu_4NMnO_4$ in toluene shows reasonable isosbestic points despite the colloidal product (Figure 3). First-order plots were slightly curved downward, so initial rates were used. Similar data were obtained for more reactive substrates, with correction for the toluene solvent oxidation. Reaction in toluene-d_8 is 6(±1) times slower than in C_7H_8 at 45 °C. All of the data are consistent with the simple bimolecular rate law (eq 5).[35] Reactions in

$$\frac{d[^{n}Bu_4NMnO_4]}{dt} = -k_2[^{n}Bu_4NMnO_4][\text{substrate}] \quad (5)$$

o-dichlorobenzene showed similar rate constants, although the reproducibility was not good. Given the difference in dielectric constant, the similarity in rates between toluene (ϵ 2.4) and *o*-$C_6H_4Cl_2$ (ϵ 9.9) rules out electron transfer or hydride transfer mechanisms. These mechanisms are also unlikely on the basis of substituent effects, for instance that the electron deficient 4-methylbenzophenone reacts faster than toluene. The disappearance of $^{n}Bu_4NMnO_4$ in toluene is faster in the presence of dioxygen, under conditions where $[O_2] > [MnO_4^-]$ so that diffusion-limited radical trapping by O_2 can compete with the equally fast reaction of carbon radicals with MnO_4^-.[38] This result suggests the intermediacy of carbon radicals, though detailed interpretation is clouded by the variety of intermediates likely present.

The strongest evidence for a mechanism of initial hydrogen atom transfer is the Polanyi correlation of rates and activation parameters with C−H bond strength (Figure 4). As found for CrO_2Cl_2, oxidations of primary, secondary, and tertiary C−H bonds all fit on the same line, indicating that steric effects are present only to the extent that they change D(C−H). Xanthene is a much better electron donor and forms a much more stable carbocation than its hydrocarbon counterparts, yet it is oxidized at a rate predicted by its homolytic C−H bond strength. The $\Delta H^{\ddagger}$ vs $\Delta H°$ plot is the most appropriate presentation, as both are enthalpies (the unitless slope is 0.8). But we prefer the correlation of log k (proportional to $\Delta G^{\ddagger}$) with $\Delta H°$ because the rate constants are more accurately

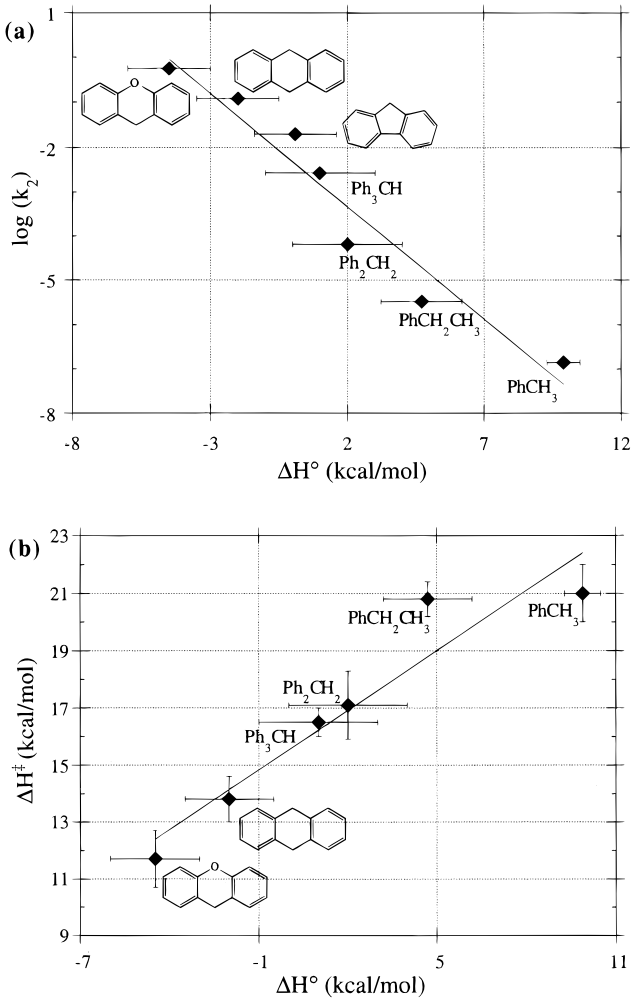


FIGURE 4. Plots of (a) log k vs $\Delta H°$ and (b) $\Delta H^{\ddagger}$ vs $\Delta H°$ for the hydrogen atom transfer step in $^{n}Bu_4NMnO_4$ reactions. Adapted from ref 35.[30]

determined and because this facilitates comparisons with main group radicals (see below). Comparable linearity is observed in the correlations with $\Delta H^{\ddagger}$ and log k because $\Delta S^{\ddagger}$ is roughly constant ($^{n}Bu_4NMnO_4$) or proportional to $\Delta H^{\ddagger}$ (CrO_2Cl_2). The correlations are however limited by the difficulty in compiling a consistent set of C−H bond strengths.

Understanding the Rate Constants: The H−OMnO$_3^-$ Bond Strength

The correlations of rate constants with C−H bond strengths are strong evidence for rate-limiting H-atom transfer. They do not, however, provide insight into *why* CrO_2Cl_2 and MnO_4^- can abstract hydrogen atoms. As noted above, it has been common to assume that such reactivity requires unpaired spin density at the abstracting atom—in these cases, an oxo group. But CrO_2Cl_2 and MnO_4^- are d^0, closed-shell species, with no unpaired spin density anywhere. The lowest lying triplet states are too high in energy to be involved in these thermal reactions ($E_{S-T} \cong 50$ kcal/mol $\gg \Delta G^{\ddagger}$).[39] Spin density arguments would predict that CrO_2Cl_2 and MnO_4^- should not abstract hydrogen atoms, yet they do.

Scheme 5. Calculation of the O−H Bond Strength in $[O_3MnO-H]^-$ [35,41]

MnO_4^- (aq) + e$^-$ ⟶ MnO_4^{2-} (aq)
1/2 H_2 (g) ⟶ H^+ (aq) + e$^-$ } E° = 0.564 V

MnO_4^{2-} (aq) + H^+ (aq) ⟶ $HMnO_4^-$ (aq) pK_a = 7.4

H• (aq) ⟶ 1/2 H_2 (g) C = -57 ± 2 kcal/mol*

MnO_4^- (aq) + H• (aq) ⟶ $HMnO_4^-$ (aq) ΔH° = -80 ± 3 kcal/mol

*C = ΔH°{H• (g) → $\frac{1}{2}H_2$ (g)} - ΔH°{H• (g) → H• (aq)} - $\frac{1}{2}$ TS°{H_2 (g)}

Table 2. X−H Bond Strengths for Hydrogen Atom Abstracting Agents[30]

X	D(X−H) (kcal/mol)	X	D(X−H) (kcal/mol)
OH•	119	Br•	87
RO•	105	[MnO_4^-]	80
Cl•	103	I•	71
ROO•	89		

The Polanyi correlations provide a better rationale for the observed reactivity. CrO_2Cl_2 and MnO_4^- are reactive because they can make a strong bond to a hydrogen atom, and reactivity correlates with bond strengths and $\Delta H°$ for H-atom transfer. Chlorine atoms are very reactive hydrogen atom abstractors, while iodine atoms are essentially inert not because of differences in spin density but because the Cl• reactions are 32 kcal/mol more exothermic (a difference in K_{eq} of $\sim 10^{23}$). Similarly, OH• reacts orders of magnitude faster than ^{t}BuO• because the H−OH bond is 15 kcal/mol stronger than the H−O^{t}Bu bond.

The O−H bond strength in $HMnO_4^-$—$\Delta H°$ for adding H• to MnO_4^-—can be calculated from a thermochemical cycle (Scheme 5) following work by Bordwell and others on organic X−H bond strengths.[40] This cycle is conceptually simple but contains a number of pitfalls, some of which we have fallen into (see footnote 41). Thermochemical cycles are path independent, so the electron of H• can be added first and then the proton. The free energies for adding the electron and proton are related to the $MnO_4^{-/2-}$ redox potential and the $-pK_a$ of $HMnO_4^-$. These values give $\Delta G° = -23$ kcal/mol for MnO_4^-(aq) + $^1/_2H_2$(g) → $HMnO_4^-$(aq). An O−H bond strength of 80 ± 3 kcal/mol is derived from this free energy by addition of a constant C and by assuming equal entropies for MnO_4^- and $HMnO_4^-$.[40] Values of C were available for measurements in DMSO and in acetonitrile.[40] For aqueous solutions with E vs NHE, we find $C = 57 \pm 2$ kcal/mol, both from tabulated thermochemical values as in Scheme 5 and using phenol and aniline as benchmarks.[35] Wiberg and Foster used a similar cycle in 1961 to estimate the enthalpy of $R_3CH + H^+ + HCrO_4^- \rightarrow R_3C^• + H_3CrO_4$ as +19 kcal/mol.[21b]

The O−H bond in $HMnO_4^-$ is somewhat weaker than H−Br and H−OO^{t}Bu but stronger than H−I (Table 2). If Br• and ^{t}BuOO• will abstract hydrogen atoms from toluene, why should not permanganate? *This bond strength approach provides new qualitative understanding of the H-atom abstracting ability of a metal-containing active site.* Thinking in this direction rather than about radical character has led us and others in new directions as described in the next section. The MnO_4^- and CrO_2Cl_2 reactions can be viewed as examples of "molecule-assisted homolysis", organic reactions in which two radicals are formed from closed shell molecules. Such reactions have been discussed for some time, recently and elegantly by Rüchardt and co-workers.[42]

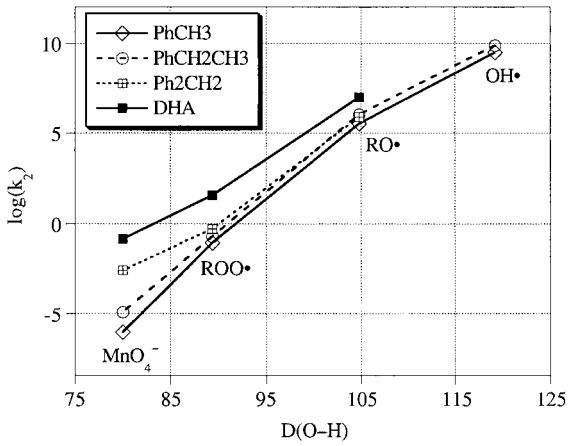


FIGURE 5. Rate constants for hydrogen atom abstraction by HO•, RO•, ^{t}BuOO•, and MnO_4^- vs the strength of the O−H bond formed for toluene, ethylbenzene, diphenylmethane, and dihydroanthracene. Adapted from ref 35.[30]

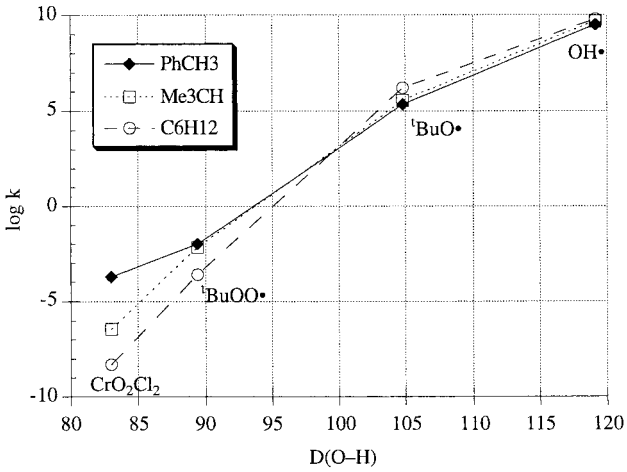


FIGURE 6. Rate constants for hydrogen atom abstraction vs the strength of the O−H bond formed, with D(H−OCr(O)Cl_2) assumed to be 83 kcal/mol. Adapted from ref 20.[30]

The bond strength approach can give a *quantitative prediction of rate constants*, based on the Polanyi equation (Figure 2). A plot of log k vs the O−H bond strength of the abstractor (Figure 5) shows that permanganate abstracts H• at essentially the rates expected for an oxygen radical that would make an 80 kcal/mol O−H bond. This occurs even though permanganate is not a radical. Similar correlations hold for CrO_2Cl_2 if the O−H bond strength is taken to be 83 kcal/mol (Figure 6). The nonlinearity of the plots is due in part to the hydroxyl radical rates approaching the diffusion limit. In addition, the dependence of rate on driving force is probably closer to

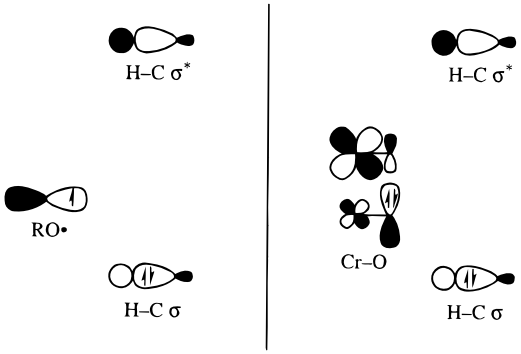


FIGURE 7. Frontier orbitals for hydrogen atom abstraction by alkoxyl radicals (left) and a metal oxo complex (right). The vertical axis gives the approximate energy spacing. Reprinted from ref 20. Copyright 1995 American Chemical Society.

quadratic, as can be seen in Figure 2 and as expected by analogy with Marcus theory.[43]

It is in some ways remarkable that the correlations in Figure 5 work as well as they do. The aqueous permanganate bond strength is assumed to apply to ion-paired toluene solutions of $^{n}Bu_4NMnO_4$. Permanganate is compared with oxygen radicals because they all form O−H bonds, but it is not clear that this is appropriate. Rates for different types of abstractors fall on different lines (Figure 2), as has been explained by frontier orbital (and other) arguments.[44] The orbitals for interaction of a metal−oxo complex with a C−H bond are quite different than in the oxygen radical case (Figure 7). Marcus theory, which has been applied to atom and group transfer reactions,[45] suggests a role for inner-sphere reorganization energies, but these are unlikely to be the same for permanganate and oxygen radicals. Such issues (discussed in more detail elsewhere[41c]) need to be addressed through studies of a range of oxidants and substrates.

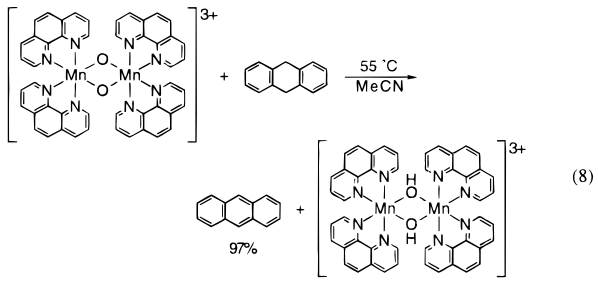
Extensions to Coordination Complexes

The importance of bond strengths in hydrogen atom abstraction reactions is not limited to metal−oxo complexes. In principle, any active site with affinity for an electron and a proton should be able to react in this fashion. This should include coordination complexes, metal−oxide active sites in heterogeneous catalysts, and active sites in metalloenzymes. Our ongoing efforts to test these ideas are summarized below.

Bis(μ-oxo)dimanganese complexes have long been studied as models for the oxygen-evolving complex in photosystem II.[46] Recent work suggests that the manganese cluster in the enzyme is oxidized by hydrogen atom transfer to a tyrosyl radical.[47] Redox potential and pK_a measurements for the $Mn^{IV}Mn^{III}$ phenanthroline complex $[Mn_2(\mu\text{-}O)_2(phen)_4]^{3+}$ yielded the O−H bond strengths in eqs 6 and 7 (using Scheme 5 with Tilset and Parker's constant for MeCN[40c]) and led us to predict hydrogen atom abstracting reactivity. Kun Wang showed that the prediction was correct: $[Mn_2(\mu\text{-}O)_2(phen)_4]^{3+}$ oxidizes dihydroanthracene (DHA) to anthracene in high yield over 11 h at 55 °C (eq 8; traces of anthrone and anthraquinone are also formed).[48]

$$[L_2Mn(\mu\text{-}O)_2MnL_2]^{3+} + H^{\bullet} \xrightarrow[MeCN]{\text{-79 kcal/mol}} [L_2Mn(\mu\text{-}O)(\mu\text{-}OH)MnL_2]^{3+} \quad (6)$$

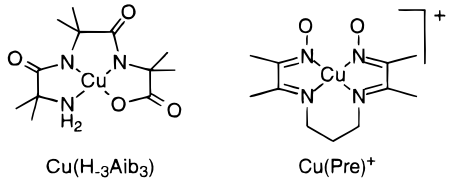
$$[L_2Mn(\mu\text{-}O)(\mu\text{-}OH)MnL_2]^{3+} + H^{\bullet} \xrightarrow[MeCN]{\text{-75 kcal/mol}} [L_2Mn(\mu\text{-}OH)_2MnL_2]^{3+} \quad (7)$$



(8)

Kinetic and mechanistic studies indicate a pathway of initial hydrogen atom abstraction from the weak C−H bond, with a deuterium isotope effect $k_{DHA}/k_{d_{12}-DHA}$ of 4.2 ± 0.3 at 55 °C and formation of bifluorenyl and 9-fluorenone from fluorene. Both the starting $Mn^{IV}Mn^{III}$ dimer and the $Mn^{III}Mn^{III}$ dimer $[Mn_2(\mu\text{-}O)(\mu\text{-}OH)(phen)_4]^{3+}$ are found to abstract hydrogen atoms from DHA. *The rate constants for both oxidants are within a factor of 10² of the values predicted* by linear extrapolation of the rate constants for $^{t}BuO^{\bullet}$ and $^{sec}BuOO^{\bullet}$ (Figure 8). The correlation among the three manganese values in the figure, however, is not very good. A much larger deviation from the bond strength prediction is the total lack of oxidation of DHA by $Mn^{IV}_2(\mu\text{-}O)_2(X\text{-}salpn)_2$ complexes, generously provided by Baldwin and Pecoraro.[49,50] These complexes are comparable to $[Mn_2(\mu\text{-}O)_2(phen)_4]^{3+}$ in the strengths of the O−H bonds they can form; perhaps they are somewhat more sterically encumbered.

The copper(III) complexes $Cu(H_{-3}Aib_3)$[51] and $Cu(Pre)^{+}$ [52] are being studied as potential functional models



for the reactive copper site in dopamine β-hydroxylase.[7] $E°$ and pK_a values for their proton-coupled electron transfer to copper(II) species predict H-atom abstraction reactivity. $Cu(Pre)^{+}$ oxidizes dihydroanthracene to anthracene in ca. 50% yield. It is not yet clear whether the mechanism is $H^{\bullet}$ abstraction.[53] $Cu(H_{-3}Aib_3)$ is inert to substrates with weak C−H bonds, although it does oxidize 2,4-di-*tert*-butylphenol.[54] Deviations from the simple correlations are expected for these systems because reduction of square planar d^8 Cu^{III} gives pseudo-octahedral d^9 Cu^{II} with bound solvent molecules, implying a solvent dependence on the bond strengths and significant entropic effects.[55] Also the reduced oxime complex has a hydrogen bond between the oxime oxygens, which contributes to the thermodynamic driving force but probably does not stabilize the H-atom transfer transition state.

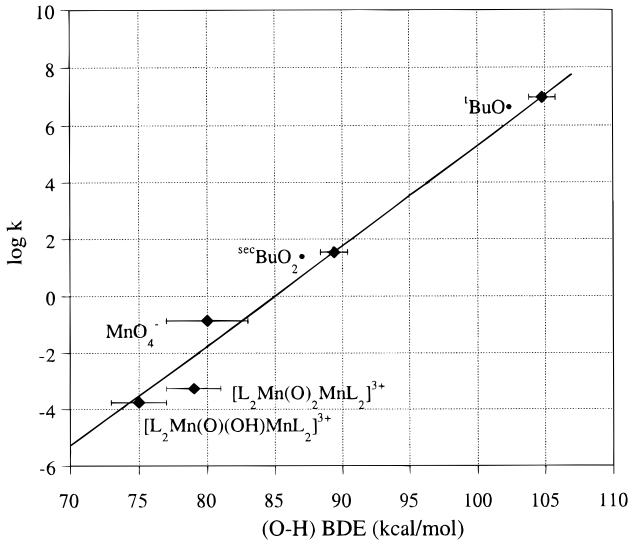


FIGURE 8. Rate constants for hydrogen atom abstraction from dihydroanthracene vs the strength of the O−H bond formed by oxygen radicals and manganese complexes. The straight line is defined by the values for ^{t}BuO• and ^{sec}BuOO•. Reprinted from ref 48. Copyright 1997 American Chemical Society.

The Fe^{III}/Fe^{II} redox couple appears to be better behaved, both in preliminary work in our laboratories[56] and in a recent communication by Jonas and Stack.[6] These workers showed that an iron(III)−methoxide complex with a pentadentate polypyridine ligand oxidizes substrates with weak C−H bonds, forming the corresponding iron(II) methanol compound. This is an interesting model for lipoxygenase enzymes. The reported redox potential and pK_a values are consistent with ability of the complex to abstract H•, and the rate constants correlate with substrate C−H bond strengths. More work of this kind is needed to test the generality and predictive power of the bond strength approach to metal-mediated hydrogen atom abstraction reactions.

Concluding Remarks

Hydrogen atom transfer reactions have traditionally been the province of main group radicals such as RO• and Cl•. This intuition has been carried over to metal-containing active sites, implying that there must be unpaired spin density at the abstracting atom. Studies of CrO_2Cl_2 and MnO_4^- oxidations, however, show that unpaired spin density is not required for hydrogen atom abstracting reactivity. Such reactivity is rooted in the strength of the bond the oxidant makes with H•. A high affinity for H• requires an oxidizing metal center and the reduced form must have significant basicity, as quantified by the $E°$ and pK_a values. Favorable or only slightly unfavorable thermochemistry is a *necessary condition* for hydrogen atom transfer because $\Delta G^{‡}$ is always greater than $\Delta G°$ (and $\Delta H^{‡} \gtrsim \Delta H°$).

The thermochemical approach provides both qualitative insight and *quantitative predictions of rate constants*, following the Polanyi correlation of log k with $\Delta H°$ for similar substrates. The predictions are reasonably accurate for $^{n}Bu_4NMnO_4$, $[Mn_2(\mu\text{-}O)_2(phen)_4]^{3+}$, $[Mn_2(\mu\text{-}O)(\mu\text{-}OH)(phen)_4]^{3+}$, and apparently for CrO_2Cl_2. In these systems, the ground-state thermodynamics are a sufficient condition for reactivity. In other systems, there is evidence that the reactivity is less than that predicted by Polanyi correlations and that other factors are important. But even here, the thermochemistry is the key starting point, as it is, for instance, in the analysis of electron transfer reactions. While more work is needed to explore the generality of the Polanyi correlations, this approach should provide a basis for a broad understanding of transition metal-mediated hydrogen atom transfer reactions, including reactions of small molecules, enzyme active sites, and reactive centers on heterogeneous catalysts.

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