Stoichiometric oxidations of \( \sigma \)-bonds: Radical and possible non-radical pathways

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Abstract

Many transition metal complexes accomplish or catalyze the oxidation of C–H, O–H, and other \( \sigma \)-bonds. Under aerobic conditions, metal complexes typically modulate an autoxidation radical chain. In anaerobic reactions, a metal complex can be the reactive species that attacks the \( \sigma \)-bond, in many cases by abstracting a hydrogen atom from the substrate. Examples described here include the oxidation of alkylaromatic compounds by ruthenium oxo complexes and reactions of deprotonated iron(III) complexes. In general, these reactions occur with addition of \( \text{H}^+ \) to a ligand and \( e^- \) to the metal center. Rate constants for such hydrogen-atom transfer reactions can, in many cases, be predicted by the Marcus cross relation. Autoxidation and metal-mediated radical mechanisms are so prevalent that proposals of non-radical oxidations of C–H bonds carry a higher burden of proof. It is argued here that the oxidation of H\(_2\) by OsO\(_4\) occurs by a non-radical, \([3 + 2]\) mechanism. OsO\(_4\) oxidizes alkanes under similar aqueous conditions. For example, isobutane is oxidized to tert-butanol, and cyclohexane to adipate and succinate. The alkane oxidations do not have the hallmarks of a radical mechanism but sufficient questions remain that a radical pathway cannot be excluded at this time.

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1. Introduction

The selective oxidation of C–H bonds in alkanes and alkylaromatic compounds is of great technological and fundamental interest. Many laboratories have taken a variety of approaches to this challenge, using homogeneous or heterogeneous catalysis, and metal- or non-metal-mediated processes. The various methodologies used include solid state, superacid, free-radical, biomimetic, and organometallic chemistries. Were this a simple problem, the effort expended would have solved it many times over.

Whenever chemical transformations are challenging, as in selective oxidations, mechanistic issues often come to the fore. A good illustration of the importance of mechanisms is the contrasting products in the oxidations of alkylaromatics by permanganate versus ruthenium tetroxide. MnO\(_4^-\) and RuO\(_4\) are isoelectronic and isostructural, and both are strong oxidants. Yet MnO\(_4^-\) reacts quite selectively at the alkyl group of an alkylaromatic (Eq. (1)) while RuO\(_4\) preferentially oxidizes the aromatic ring (Eq. (2)) [1]. The origin of this dichotomy is mechanistic:

\[ \text{MnO}_4^- + \text{C}_n	ext{H}_{2n+1} \rightarrow \text{C}_n\text{H}_{2n}^+ + \text{OH}^- \] (1)

\[ \text{RuO}_4^2^- + \text{C}_n\text{H}_{2n+1} \rightarrow \text{C}_n\text{H}_{2n}^+ + \text{RuO}_4^- + \text{H}_2 \] (2)
MnO$_4^-$ acts as a hydrogen-atom abstractor while RuO$_4$ acts as an electrophile. In our view, achieving selective oxidations of C=H and other σ-bonds will require mechanistic understanding and control.

The predominant mechanism in metal-mediated C=H bond oxidations is hydrogen-atom transfer (HAT). There are other important mechanisms which are receiving much study, most prominently organometallic and electrophilic approaches in which the C=H bond binds to an electrophile, as in “Shilov chemistry” with platinum complexes [2–4]. However, most practiced metal-mediated C=H bond oxidations occur by initial removal of H* from the substrate: X + R-H → XH + R* [5,6]. Examples include high temperature reactions on metal oxide surfaces, enzymatic oxidations, biomimetic model systems, and homogeneous catalysis by metal salts. In some cases the role of the metal is to mediate a radical chain process, and the abstraction of H* from the C=H bond is accomplished by an oxyl, halogen, or other main-group radical. The cobalt, manganese, and/or bromide-catalyzed oxidations of p-xylene, cyclohexane, and other hydrocarbons are classic examples which are practiced industrially on very large scales [3]. In these processes, the primary radical abstractors are thought to be RO*, ROO*, and Br*.

Aerobic oxidations catalyzed by metal oxide surfaces appear to involve hydrogen-atom transfer to the surface as the initiator for gas-phase radical chains [3,7]. Similar metal-initiation of autoxidation radical chains are also common for solution reactions [5].

The direct abstraction of H* by metal complexes or active sites may serve as an initiation step or – particularly in stoichiometric or enzymatic reactions – can be the key substrate activation step. These reactions can be written schematically as in Eq. (3).

\[ \text{L}_n\text{M}^{\text{n}+} + \text{H} → \text{L}_n\text{M}^{\text{n}+\text{H}^-} \]

Addition of H* to a metal complex typically results in protonation of a ligand and reduction of the metal center. In a formal sense, H* is separated into its component H* and e\textsuperscript{−}. These reactions thus fall under the more general topic of proton-coupled electron transfer (PCET) [8,9]. In our view, any oxidizing metal complex with a basic site on a ligand will act as a hydrogen-atom abstractor. The first half of this review summarizes our efforts to understand this important class of reactions.

The second half of this review describes studies of osmium tetroxide oxidations of C=H and other σ-bonds. For the reaction of OsO$_4$ with H$_2$, a pericyclic [3 + 2] mechanism is implicated. Studies on alkane oxidation by OsO$_4$ do not show the hallmarks of free-radical reactions but preliminary studies may indicate a more complex pathway than a simple [3 + 2] cycloaddition.

So many metal-mediated oxidation reactions involve hydrogen-atom abstraction that the burden of proof must lie with those who propose a different mechanism [5,6]. Work is in progress to explore the mechanism, the selectivity and scope, and possible catalytic versions of these alkane oxidations.

2. Metal-mediated hydrogen-atom transfer (HAT) reactions

Organic free-radical chemistry has been actively studied for over a century, and hydrogen-atom transfer has been one of its major themes [10]. HAT to metal complexes has been discussed by a number of workers, going back at least to Wiberg in the 1960s [11]. Our studies in this area began with mechanistic examination of the long-known oxidations of alkanes and alkylaromatic compounds by chromyl chloride (CrO$_2$Cl$_2$) [12,13] and permanganate [14]. Various lines of evidence pointed toward a mechanism of initial HAT from a C=H bond in the substrate to an oxo group of the oxidant (Eq. (4)).

\[ \text{MnO}_4^- + \text{PhCH}_3 \rightarrow \text{MnO}_3(\text{OH})^- + \text{PhCH}_2^+ \rightarrow \]

For both the Cr$^{VI}$ and permanganate oxidations, the rate constants correlated well with C-H bond strengths (another example of such a correlation is shown below). Alternative mechanisms involving initial electron transfer to give radical cations RH$^{	ext{•}+}$ or hydride transfer to give carbocations R$^+$ were ruled out by the effects of polar solvents and polar substituents. The permanganate oxidation of toluene occurs at the same rate in neat toluene and in ortho-dichlorobenzene, and the CrO$_2$Cl$_2$ oxidation of cyclohexane occurs at roughly the same rate in cyclohexane solution and in the gas phase. MnO$_4^-$ oxidation of the electron-deficient 4-methylbenzenophenone occurs faster than toluene despite the electron-withdrawing acyl substituent. The correlations with C-H bond strengths, the small solvent effects, and the substituent effects are all characteristic of HAT from hydrocarbons [10].

Metal-mediated HAT has now been implicated in a large number of hydrocarbon oxidation reactions, including coordination complexes of iron, manganese, copper, and ruthenium [9,15–27]. For example, the deprotonated iron(III)-tris(2,2'-imidazoline) complex abstracts H* from weak C-H bonds such as in xanthene (Eq. (5)) [19]. The ruthenium(IV)-oxo complex [RuO(bpy)$_3$(py)$_2$]$^2+$ (Ru$^{IV}$ + O$^{2-}$), studied in detail by Meyer and co-workers [24], reacts with a range of C-H bonds by hydrogen-atom abstraction (cf. Eq. (6)) [25–27].
As in the cases above, one indication of a hydrogen-atom transfer mechanism is the correlation of rate constants with C–H bond dissociation energies (BDEs), shown in Fig. 1. These rate constants do not correlate as well with ionization energies (IEs): for instance, RuIV = O2+ abstracts H• from cyclohexene 28 times faster than from cumene, even though cumene has a 0.22 eV lower IE. In some cases, however, rate constants will correlate almost equally well with BDEs and with IEs. This is because these two properties often correlate with each other over a series of related compounds (cf.[28,29]). It is also valuable to look at the slope of the correlation, \( \Delta G^\ddagger / \Delta G^\circ \), or equivalently \( \Delta \ln(k) / \Delta \ln(K_{eq}) \) (or \( \Delta H^\ddagger / \Delta H^\circ \), if only enthalpies are available). In an HAT mechanism, \( \Delta H^\ddagger / \Delta G^\circ \) and \( \Delta H^\ddagger / \Delta H^\circ \) should be near to 0.5. In other words, if the C–H bond of substrate A is 2 kcal mol\(^{-1}\) weaker than substrate B (\( \Delta G^\circ \) = -2 kcal mol\(^{-1}\)), then the barrier for HAT from A should be about 1 kcal mol\(^{-1}\) smaller than that from B. In an elegant use of such arguments, the mechanism of phenol oxidation by a dicopper peroxo complex has been shown to involve initial electron transfer rather than HAT [30], in part based on the very small dependence of the barrier on C–H bond strength.

The initial HAT step (e.g., Eqs. (3)–(6)) typically sets the rate and site of reaction in a C–H bond oxidation. The nature of the products and the selectivity of oxidation, however, are often determined by the trapping of the organic radical(s) formed.

Under conditions where C–H bonds are oxidized, the three primary mechanisms of radical trapping reactions are: transfer of a second hydrogen atom to give an alkene (Eq. (7)); transfer of a “soft” ligand such as a halogen (Eq. (8)); and addition to a metal oxo group (Eq. (9)). In the CrO2Cl2 oxidation of cyclohexane, all three pathways occur at comparable rates, close to the diffusion limit [12].

\[
\begin{align*}
L \text{M}^\ddagger n\text{X} + & \text{Y} \rightarrow L \text{M}^{(n+1)\text{H}-\text{X}} + \text{Y} \\
L \text{M}^\ddagger n\text{X} + & \text{R}^* \rightarrow L \text{M}^{(n+1)\text{H}^*} + \text{R} \\
L \text{M}^\ddagger n\text{O} + & \text{R}^* \rightarrow L \text{M}^{(n+1)\text{H}^*} - \text{O} - \text{R}
\end{align*}
\]

Similarly, oxidation of cumene by RuIV = O2+ gives both cumyl alcohol and \( \alpha \)-methylstyrene as primary products [26]. Carbon radicals have been shown to add to an oxo group of permanganate in an almost diffusion-limited process [31]. Dihydroanthracene is oxidized typically to anthracene, because the C–H bond in the hydroanthracenyl radical is very weak (Eq. (10)). The xanthenyl radical, because it does not have a hydrogen \( \alpha \) or \( \gamma \) to the radical center, is either trapped to xanthone or builds up to sufficient concentrations that radical dimerization to bixanthene is observed (Eq. (11)). Only xanthone is observed with MnO4\(^-\) while bixanthene is the sole product from FeIII(Hbim) (cf.Eq. (5)). Reactions with \([\text{phen}]_2\text{Mn}(\alpha\text{-O})_2(\text{phen})_2]^{3+}\) give both products [14,19]. The different products indicate that these different oxidants trap the xanthenyl radical at very different rates [20]. The origin of the differences in these rates seems likely to be steric, since addition of \( \text{R}^* \) to all three oxidants should be quite favorable with similar thermochemistry.

\[
\begin{align*}
\text{H} + L \text{M}^\ddagger n\text{MeO} & \rightarrow L \text{M}^{(n+1)\text{H}^*} \\
L \text{M}^\ddagger n\text{MeO} + & \text{R}^* \rightarrow L \text{M}^{(n+1)\text{H}^*} - \text{O} - \text{R}
\end{align*}
\]

The addition of radical traps to C–H bond oxidation reactions can redirect the products and can provide additional evidence for the intermediacy of free-radicals. Typically, only oxidative radical traps can be used because reductive and unsaturated traps such as \( \cdot \text{Bu}_3\text{SnH}, \text{hydroquinone, BHT,} \text{2,6-} \text{Bu}_2-4\text{MeC}_6\text{H}_2\text{OH} \) and alkenes are usually more reactive with the oxidant than even a weak C–H bond. CBrCl3 is an effective trap, for instance, converting cyclohexyl radical to C6H11Br with \( k = 2 \times 10^7 \text{M}^{-1}\text{s}^{-1} \) [12], although the CCl3• formed is reactive and can propagate radical chains. With any radical trap,
a negative result (no changes in rate or products) must be interpreted with caution unless the relevant rate constants indicate that the trap should intercept a radical intermediate faster than the added oxidant [9]. Any reagent involved in the transfer of H + and e − has two relevant redox potentials E ¯ and E o for the protonated and deprotonated species, and two pKa values, for the oxidized and reduced forms (Scheme 1). Only three of these four values are independent because the energy to go all the way around the square totals zero, as expressed algebraically in Eq. (12).

\[
(E_{\Delta H^\circ} - E_{\Delta G}) = \left( \frac{2.3RT}{F} \right) \left[ p_{K_a}(AH^+) - p_{K_a}(AH) \right] \tag{12}
\]

The thermochemical affinity of reagent A for H+ is given by the diagonal of Scheme 1 [35,36]. The cycle is completed with a constant C accounting for the formation of H+ (Eqs. (13)–(17), in kcal mol−1). C is independent of A/AH but does depend on the solvent and choice of reference electrode for E° [36]. E° and Ks are free energies so this cycle gives the bond dissociation free energy (BDE) of AH, with C = −23.06E°(H+) [35].

\[
A \rightarrow \cdot \rightarrow A^- \rightarrow E^-(A) \tag{13}
\]

\[
A^- + H^+ \rightarrow A \cdot \rightarrow -p_{K_a}(AH) \tag{14}
\]

\[
H^+ \rightarrow \cdot \rightarrow H^+ \rightarrow C \tag{15}
\]

\[
A \rightarrow H^+ \rightarrow AH \tag{16}
\]

\[
\Delta G(AH) = A + H^+ = -23.06E°(A) + 1.37p_{K_a}(AH) + C = -23.06E°(AH^+) + 1.37p_{K_a}(AH^+) + C \tag{17}
\]
$k \leq 10^8 \text{M}^{-1}\text{s}^{-1}$ for reaction with $\text{BuO}^+$ [44]. Oxidizing metal complexes behave similarly, with acetonyliron being an excellent inert solvent. For instance, Que and co-workers have found that $[\text{[Bn-tpenFeV(O)]]^2+}$ is unreactive with $\text{MeCN}$ even though it oxidizes cyclohexane $[\Delta G(\text{H}-\text{H}) = 99 \text{ kcal mol}^{-1}]$ [17]. This has been examined in a recent computational study [45]. The low reactivity of the hydrogen atoms in $\text{MeCN}$ and other acidic ($\delta^+$) $\text{C}-\text{H}$ bonds toward abstraction by electrophilic radicals has often been ascribed to a ‘polar effect’ [10,41]: an abstractor such as an oxyl radical reacts faster with electron rich $\text{C}-\text{H}$ bonds and more slowly with electron-poor bonds.

We have found that rate constants for HAT reactions in many cases follow Marcus Theory, in particular the Marcus cross relation (Eq. (18)) [46]; for a more complete discussion, see [9,42,47].

\[ k_{\text{ST}} = \frac{k_{\text{XX}}k_{\text{YY}}}{k_{\text{XY}}k_{\text{YX}}} \]  

Eq. (18) uses the free energy of reaction (in the form of the equilibrium constant $K_{\text{XY}}$) and the so-called self-exchange rate constants $k_{\text{XX}}$ and $k_{\text{YY}}$ for the degenerate reactions such as $X + HX \rightarrow X + X$ ($f_G$ is typically close to 1). The $\sim 10^8$ faster reactions of $\text{O}-\text{H}$ bonds versus $\text{C}-\text{H}$ bonds of comparable strength are seen to trace from the $\sim 10^6$ faster HAT self-exchange rate constants for $\text{O}-\text{H}$ bonds. The Marcus approach also explains why abstractions by most metal complexes correlate with those of oxygen radicals: these reagents all have similar intrinsic barriers for HAT, as indicated by self-exchange rates. Some metal complexes have quite different intrinsic barriers, however. The cobalt/biimidazoline analogs of the iron complexes in Eq.(5) have large intrinsic barriers due to the substantial reorganization upon reduction of low-spin Co$^{III}$ to high-spin Co$^{II}$ [47]; these compounds are relatively unreactive toward HAT.

All of the reactions above have been described as hydrogen-atom transfers, in other words, as concerted (one-step) transfers of a proton and an electron. It should be noted, however, that such transfers $\text{AH} + \text{B} \rightarrow \text{A} + \text{BH}$ can also occur by stepwise mechanisms, as discussed in more detail elsewhere (Scheme 2; compare Scheme 1) [9,48]. Initial proton transfer (PT) to give $\text{A}^+ + \text{BH}^-$ could be followed by electron transfer (ET), and initial ET to yield $\text{AH}^+ + \text{B}^-$ could be followed by PT. Examples of all of these mechanisms are known and the interplay between them can have important consequences. For instance, while the oxidation of p-xylene proceeds in excellent yields to terephthalic acid ($\delta^+$-$\text{HOO}_2\text{CC}_6\text{H}_4\text{O}_2\text{H}$) predominantly by an HAT mechanism [49], related reactions of dimethylphenanthrenes are plagued with side reactions, in part because the lower redox potential of the naphthalene leads to a competing ET pathway.

### 3. Oxidations of $\sigma$-bonds by OsO$_4$

Free-radical oxidations, as noted above, are widely practiced and can be quite selective [3]. However, for many substrates free-radical reactions are non-selective and do not give the desired products. The studies outlined above indicate that there is a close analogy between organic HAT reactions and HAT to metal complexes. The selectivity in radical reactions does not strongly depend on the nature of the abstracting group, whether it is a metal or not (other than polar effects and the general trend that more reactive reagents are less selective). Therefore, achieving selective oxidations for many substrates will require non-radical oxidation mechanisms [2,50]. Described in this section is one possible approach to non-radical oxidations, using osmium tetraoxide. The initial results on the oxidation of alkanes do not bear the hallmarks of a radical pathway, but further work is required before firm mechanistic conclusions can be reached.

The OsO$_4$-catalyzed oxidation of alkenes to cis-diols is one of the premier oxidation reactions in the chemist’s arsenal [51]. A variety of terminal oxidants can be used, including Os$_3$ [52]. The reactions are accelerated by the addition of ligands such as pyridine or tertiary amines; the famous enantioselective version uses chiral amines [53]. After much debate, there is now a broad if not complete consensus that the mechanism of these reactions involves $[3 + 2]$ addition of the alkene to a Os=Os-O unit. Computational work from a number of laboratories supports the $[3 + 2]$ path [54,55], and one particularly strong study combined computations with experimental secondary isotope effects [56]. In an interesting extension of these ideas, Collman et al. have recently described the reductions of RuO$_4$ and MnO$_4$ with H$_2$; OsO$_4$ was not reported to react [57]. Based on computations and experiments (building on previous permananate studies [58–61]), the H$_2$ reactions were concluded to occur by a $[3 + 2]$ mechanism in which the H=H $\sigma$ bond is the “2” component.

We set out to determine whether the OsO$_4 + H_2$ reaction could be accelerated by added ligands, continuing our long-term interest in oxidations by osmium complexes [62–64]. In the presence of pyridine, OsO$_4$ is readily reduced by H$_2$ in hexane, CHCl$_3$, or CCl$_4$ solution (Eq. (19)) [65].

\[ \text{OsO}_4 + \text{H}_2 \rightarrow \text{Os}^\cdot + \text{H}_2 + \text{O}_2 + \text{H}_2 \text{O} \]

![Scheme 2. Square scheme for hydrogen-atom transfer.](Image)

Under 1 bar H$_2$ in 24:1 CHCl$_3$/py, for instance, reduction is complete within 16 h at room temperature. In the absence of pyridine, there is no change in the optical spectrum of OsO$_4$ over 16 h in CHCl$_3$. The product is the well-known Os$^{IV}$ dimer, Os$_2$(O$_2$py)$_2$ [66].

OsO$_4$ is also readily reduced by H$_2$ in aqueous solutions, forming osmate (Os$_2$(O$_2$O)py$_2$) at pH $\geq$ 8 (Eq. (20)). OsO$_4$...
Fig. 3. Top: plot of second order rate constants, $k_2$, vs. pH. The line represents the best fit to $-d[\text{OsVIII}]/dt = [\text{H}_2](k_{\text{OsO}_4} + k_{\text{OsO}_4\text{OH}^-})$. The estimated second order rate constant of 0.38 M$^{-1}$ s$^{-1}$ at pH 14.60 is reduced 10 times to fit on the plot. Bottom: speciation of aqueous OsVIII. ©American Chemical Society; reproduced with permission from [65].

binds one and then two hydroxide ions at high pH, and the rate of reaction with H$_2$ accelerates with the binding of ligands.

This rate acceleration is less dramatic than is found in nonpolar solutions, as $k_{\text{OsO}_4\text{OH}^-}$ is only a factor of three faster than $k_{\text{OsO}_4}$. The variation of second-order rate constants and the speciation of OsO$_4$ are shown on the same pH scale in Fig. 3. Above pH 12.5 rate constants can only be estimated because of the competing decomposition of OsVIII. Rate constants from 8 to 68°C at pH 9.22 indicate $\Delta^f H^\ddagger = 13.2$ (2) kcal mol$^{-1}$ and $\Delta^f S^\ddagger = -22.3$ (3) cal mol$^{-1}$ K$^{-1}$ for aqueous OsO$_4$ + H$_2$. Similar values are obtained at pH 12.3 where OsO$_4$ and [OsO$_4$(OH)$_2$]$^-$ both contribute to the rate. The estimated rate constant for OsO$_4$ + H$_2$ in CHCl$_3$/py falls in between the aqueous $k_{\text{OsO}_4}$ and $k_{\text{OsO}_4\text{OH}^-}$ [65].

The free energy for the reduction of OsO$_4$(OH)$_2$$^{n-}$ with H$_2$ at a given pH is directly related to the redox potential at that pH, because aqueous redox potentials are referenced to the normal hydrogen electrode. The potentials are summarized in a Pourbaix diagram (Fig. 4) and the arrows give the $\Delta^\circ G^\ddagger$ values for reaction with H$_2$ at pH 9.2, 12.3, and $>14.2$, respectively. (The “$\ddagger$” in $\Delta^\circ G^\ddagger$ indicates standard state for all species except [H$^+$].) The reactions are more favorable at higher pH, which is one of the reasons for the ligand acceleration.

The plausible mechanisms for H$_2$ reduction of OsO$_4$, following Collman et al. [57], include initial H$^\bullet$ and H$^-$ transfers and concerted [2 + 2] and [3 + 2] cycloadditions of H$_2$ (Scheme 3). Hydride transfer from H$_2$ to give H$^+$, OsO$_4$ + H$_2$ $\rightarrow$ [OsO$_4$(OH)$_2$]$^-$ + H$^+$, is quickly ruled out by the similar rates in aqueous and low polarity organic solvents and the lack of a dependence on aqueous buffer concentration or pH (other than the effect of pH on the speciation of OsVIII).

Hydrogen-atom transfer, as discussed in the first half of this short review, depends on the bond dissociation free energies involved. The affinity of OsVIII species for H$^+$ has not been
Scheme 4. OsO\(_4\) bond dissociation free energies. ©American Chemical Society; reproduced with permission from reference [65].

precisely determined but can be estimated from the data in the Pourbaix diagram above (Fig. 4). The \(\Delta G^\circ = -27\) kcal mol\(^{-1}\) for addition of \(\text{H}_2\) to OsO\(_4\)(OH)\(_2\)^{2-}\) implies that the sum of the two BDFEs is 129 kcal mol\(^{-1}\) (Scheme 4). The putative Os\(^{VI}\) intermediate species being unstable to disproportionation means that OsVIIO\(_3\)(OH)\(_3\)^{2-}\) + H\(^*\) \(\rightarrow\) OsVIO\(_2\)(OH)\(_4\)^{2-}\) is more favorable than OsVIII\(_4\)(OH)\(_2\)^{2-}\) + H\(^*\) \(\rightarrow\) OsVIIO\(_3\)(OH)\(_3\)^{2-}\). In other words, BDFE(1) must be larger than BDFE(2) [65]. This implies that BDFE(2) < 65 kcal mol\(^{-1}\) and therefore that \(\Delta G^\circ > 30\) kcal mol\(^{-1}\). This is larger than the observed \(\Delta G^\circ\) of 20 kcal mol\(^{-1}\), ruling out HAT for \(\text{H}_2\) reduction of OsO\(_4\)(OH)\(_2\)^{2-}\) and suggesting that neither OsO\(_4\) nor OsO\(_4\)(OH)\(^{-}\) react by this mechanism.

The \(\text{[2 + 2]}\) and \(\text{[3 + 2]}\) concerted mechanisms in Scheme 3 are difficult to distinguish experimentally, as indicated by the long controversy over the mechanism of OsO\(_4\) oxidations of alkenes [51–56]. Computationally, however, many laboratories have concluded that the \(\text{[3 + 2]}\) pathway is much more favorable than the \(\text{[2 + 2]}\) for alkene oxidation [54–56]. Calculations at the B3LYP level of density functional theory (DFT) for \(\text{H}_2 + \text{OsO}_4\) shows the same strong preference for the \(\text{[3 + 2]}\) mechanism, by 40 kcal mol\(^{-1}\), respectively (Fig. 5) [65]. \(\text{H}_2\) addition to OsO\(_4\)(OH)\(^{-}\) is similar, with \(\Delta H^\circ\)\(_{\text{calc}}\)\(\text{[g]}\) = +44.6 and +10.6 kcal mol\(^{-1}\) for the \(\text{[2 + 2]}\) and \(\text{[3 + 2]}\) mechanisms. The calculations are in qualitative agreement with the measurements, especially given that the computed values are for gas phase reactions while the experimental data are from aqueous solutions. For instance, the calculated gas-phase \(\Delta H^\circ\) for OsO\(_4\) + \(\text{H}_2\) of 18.8 kcal mol\(^{-1}\) is somewhat larger than the experimental aqueous \(\Delta H^\circ = 13\) (2) kcal mol\(^{-1}\). Hydroxide binding lowers the barrier, computationally in the gas phase by 8 kcal mol\(^{-1}\), experimentally in aqueous solution by less than 1 kcal mol\(^{-1}\). \(\text{H}_2\) addition to Os\(^{VI}\) is quite favorable both by gas-phase calculations and from the electrochemical values. Although a direct comparison is not available, the computations may perhaps overestimate the favorability: for instance, \(\Delta H^\circ\)\(_{\text{calc}}\)\(\text{[g]}\) = -51 kcal mol\(^{-1}\) for OsO\(_4\)(OH\(^{-}\)) + \(\text{H}_2\) \(\rightarrow\) OsO\(_2\)(OH\(_3\))\(^{-}\) while in water, \(\Delta G^\circ = -27\) kcal mol\(^{-1}\) OsO\(_4\)(OH\(^{-}\)) + \(\text{H}_2\) + OH\(^{-}\) \(\rightarrow\) OsO\(_2\)(OH\(_2\))\(^{2-}\).

The \(\text{H-H}\) bond in \(\text{H}_2\) is comparable to or stronger than the \(\text{C-H}\) bonds in most hydrocarbons, so the facile oxidation of \(\text{H}_2\) suggested that OsO\(_4\) would also oxidize hydrocarbons in basic aqueous solutions. While alkene oxidation by OsO\(_4\) has been widely practiced, we are not aware of any report of this reagent oxidizing hydrocarbon \(\text{C-H}\) bonds (other than reports using peroxides which likely involve RO\(^{-}\) [67,68]). RuO\(_4\) oxidizes alkanes under fairly mild conditions and a \(\text{[3 + 2]}\) mechanism has...
H oxidations are bonds of isobutane under these conditions. In the absence of organic substrate, there is buffer does not significantly affect the oxidation of isobutane. In cis equivalents of Os VIII butanol over a week a 85 \( ^\circ \text{C} \) sodium phosphate buffer, react with 10 bar isobutane to give OsO4 are quite small, the oxidation stoichiometry requires 5 oxidation by OsO4 suggest that barriers for C oxidation of adipate is observed 37 \( \pm \) 7% for succinate, which is likely oxidized to malonate \( \text{O}_2\text{C}(-\text{CO}_2\text{H})_2 \rightarrow \text{CO}_2 \). Preliminary studies indicate that cis-9-decalin would have been observed if it were formed, so this experiment suggests that hydroxylation is stereoselective. Related stereo-retentive hydroxylation of cis- and trans-decalins by RuO4 were taken as evidence for a concerted \( [3 + 2] \) mechanism.

OsO4 oxidations of alkenes can be run in catalytic fashion with a variety of terminal oxidants [51]. Many of these oxidants would themselves be consumed under the more forcing conditions used here, such as N-methyl morpholine N-oxide (NMO), H2O2, and ferricyanide. For safety reasons, we have hesitated to heat gas mixtures of alkanes and O2 in the presence of OsO4. Our preliminary efforts at catalytic reactions have used periodate, IO4-. Periodate also acts as a buffer, with 0.1 M solutions being pH 4.3. Four and a half equivalents of isobutane are oxidized by 3.4 mM OsO4 and 170 mM NaIO4 over 168 h at 85 \( ^\circ \text{C} \) (Eq.(23)), indicating a mildly catalytic reaction. Under these acidic conditions, somewhat different alkane oxidation products are observed, isobutane forming acetic acid and isobutyric acid (Me2CHCO2H) in addition to t-butanol. At lower temperature, acetone is observed, presumably more stable at pH 4.3 than at pH 12.3 because of the lower formation of the enol/enolate. The isobutyric acid could arise from attack at a methyl group, or by dihydroxylation of isobutylen and carboxylation rearrangement (Eq.(24)).

Mechanistic studies of these alkane oxidations are ongoing.

It seems very unlikely that these are autooxidation reactions as no O2 or peroxides are present in the initial reaction mixtures; the formation of O2 from OsO4 occurs only at very high pH. Hydroxyl radical is not the reactive oxidant based on the tertiary selectivity of isobutane oxidation: OH+ (aq) reacts competitively with the primary and tertiary C-H bonds of isobutane [77] and is quite reactive with \(^{\text{1}}\text{BuOH} \) which is essentially inert...
under our conditions. The thermochromy discussed above suggests that OsO\(_4\)(OH)\(_2\) do not have sufficient affinity for H\(_2\) to abstract from cyclohexane, although parallel computational work is in progress. On the basis of these data, we proposed that the alkane reactions occur by a \([3 + 2]\) mechanism analogous to that proposed for RuO\(_4\) [73] and that found for H\(_2\) + OsO\(_4\) and H\(_2\) + RuO\(_4\) [57, 65]. Recent work, however, sug-
gests that the reactions may be mechanistically more complex than a simple bimolecular reaction between an oxospecies and the alkane. More studies are needed to determine whether these reactions are among the rare exceptions to the generaliza-
tion that metal-mediated hydrocarbon oxidations involve radical mechanisms.

4. Conclusions

Metal-mediated oxidations of C–H and other σ-bonds most often involve free-radical intermediates. Metal complexes can mediate organic radical chain processes, particularly in the pres-
ence of air or other sources of O\(_2\). Metal complexes can also abstract hydrogen atoms directly from C–H bonds. The rates of such abstractions in many cases correlate well with the driv-
ing force, as determined from the C–H bond strength and the thermochemical affinity of the metal complex for H\(_2\). Other factors such as polar effects and intrinsic barriers to hydrogen-atom transfer can also play a role. There is much interest in finding non-radical pathways for σ-bond oxidations because of the different selectivity that would be obtained. The oxidation of H\(_2\) by OsO\(_4\) pro-
ceeds by a pericyclic \([3 + 2]\) mechanism, analogous to the related reaction of RuO\(_4\) [57]. Alkanes are also oxidized by OsO\(_4\) under fairly mild conditions (aqueous base, 85 °C). The alkane oxidations do not show the hallmark of a radical pathway but, given the prevalence of radical mechanisms, more studies are needed before this can be considered a firm conclusion.

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