Stoichiometric oxidations of σ-bonds: Radical and possible non-radical pathways

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Available online 23 March 2006

Abstract

Many transition metal complexes accomplish or catalyze the oxidation of C−H, O−H, and other σ-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 σ-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 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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Keywords: Oxidation; Hydrogen-atom abstraction; Radicals; Osmium tetroxide; Marcus theory

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:

(1)

(2)
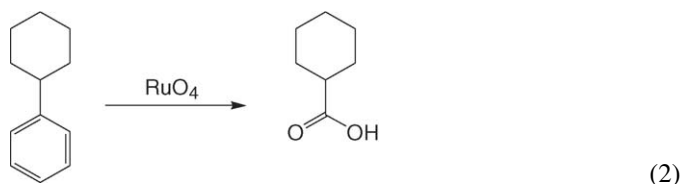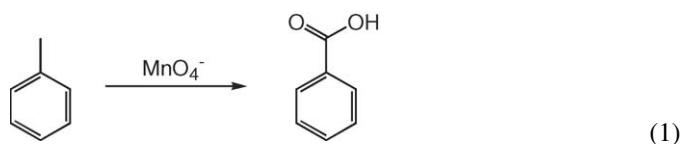
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MnO_4^- reacts as a hydrogen-atom abstractor while RuO_4 acts as an electrophile. In our view, achieving selective oxidations of C−H and other σ-bonds will require mechanistic understanding and control.

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 $H^\bullet$ from the substrate: $X + R–H \rightarrow XH + R^\bullet$ [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 $H^\bullet$ 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 $RO^\bullet$, $ROO^\bullet$, and $Br^\bullet$. 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 $H^\bullet$ 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).

$$L_nM^{n+}–X\text{:} + H–R \rightarrow L_nM^{(n-1)+}–XH + R^\bullet \qquad (3)$$
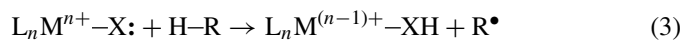
Addition of $H^\bullet$ to a metal complex typically results in protonation of a ligand and reduction of the metal center. In a formal sense, $H^\bullet$ is separated into its component H^+ and e^-. These reactions thus fall under the more general topic of proton-coupled electron transfer (PCET) [8,9]. 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 alkyl-aromatic compounds by chromyl chloride (CrO_2Cl_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)).

$$MnO_4^- + PhCH_3 \rightarrow Mn(O)_3(OH)^- + PhCH_2^\bullet \rightarrow \rightarrow \qquad (4)$$
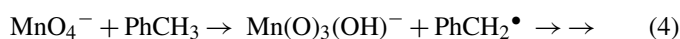
For both the Cr^{VI} and permanganate oxidations, the rate constants correlated well with C−H bond strengths (another example of such a correlation is shown below). Alternative mechanisms involving initial electron transfer to give radical cations $RH^{\bullet+}$ or hydride transfer to give carbocations 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_2Cl_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-methylbenzophenone 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′-bi-imidazoline) complex abstracts $H^\bullet$ from weak C−H bonds such as in xanthene (Eq. (5)) [19]. The ruthenium(IV)-oxo complex $[Ru(O)(bpy)_2(py)]^{2+}$ (**$Ru^{IV}=O^{2+}$**), 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].
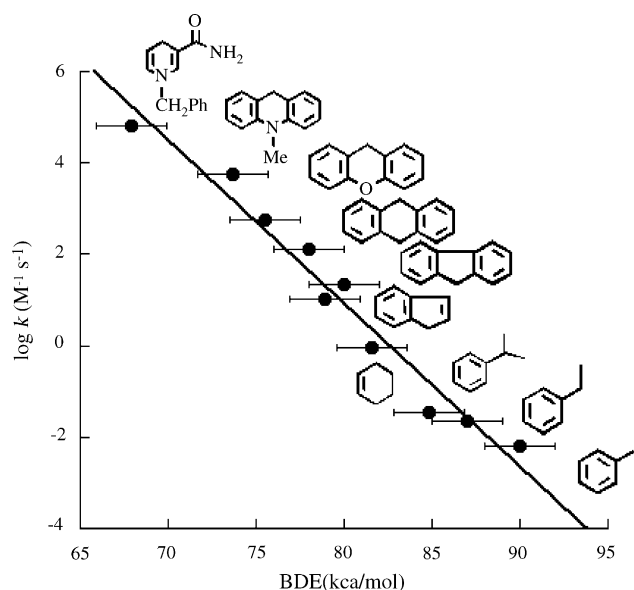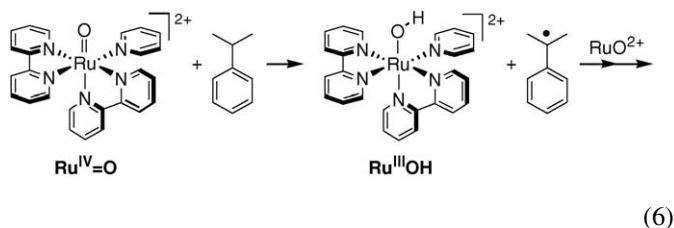

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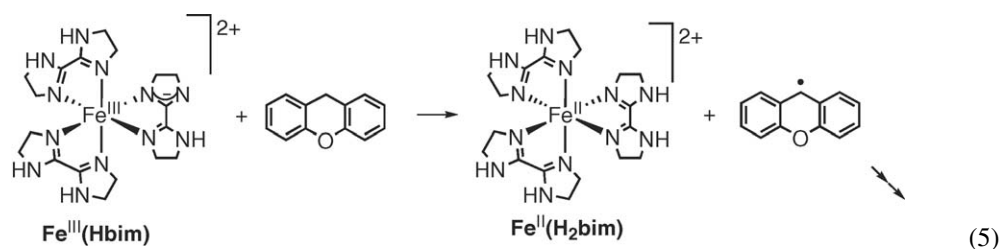
Fig. 1. Plot of rate constants for oxidations by $\mathbf{Ru^{IV}O^{2+}}$ vs. C−H bond energies (BDEs) (adapted from [27]).


(6)

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, $\mathbf{Ru^{IV} = O^{2+}}$ abstracts H$^{\bullet}$ 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, $\partial\Delta G^{\ddagger}/\partial\Delta G^{\circ}$ or equivalently $\partial\ln(k)/\partial\ln(K_{eq})$ (or $\partial\Delta H^{\ddagger}/\partial\Delta H^{\circ}$ if only enthalpies are available). In an HAT mechanism, $\partial\Delta G^{\ddagger}/\partial\Delta G^{\circ}$ and $\partial\Delta H^{\ddagger}/\partial\Delta H^{\circ}$ 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 ($\Delta\Delta G^{\circ} \cong -2$ 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 O−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.
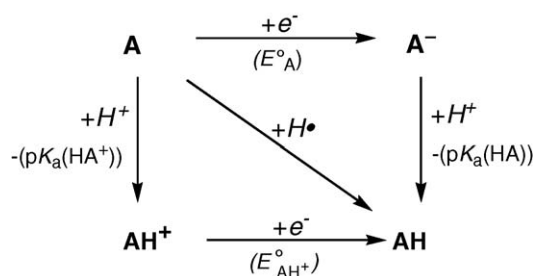
Under conditions where C−H bonds are oxidized, the three primary mechanisms of radical trapping reactions are: transfer of a second hydrogen atom to give an alkene (Eq. (7)); transfer of a "soft" ligand such as a halogen (Eq. (8)); and addition to a metal oxo group (Eq. (9)). In the CrO$_2$Cl$_2$ oxidation of cyclohexane, all three pathways occur at comparable rates, close to the diffusion limit [12].

(7)

(8)

(9)
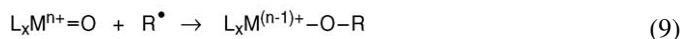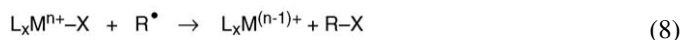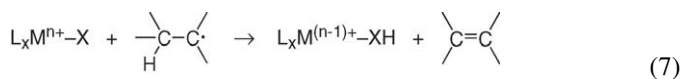
Similarly, oxidation of cumene by $\mathbf{Ru^{IV} = O^{2+}}$ gives both cumyl alcohol and α-methylstyrene as primary products [26]. Carbon radicals have been shown to add to an oxo group of permanganate in an almost diffusion-limited process [31]. Dihydroanthracene is oxidized typically to anthracene, because the C−H bond in the hydroanthracenyl radical is very weak (Eq. (10)). The xanthenyl radical, because it does not have a hydrogen α or γ 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 MnO$_4^{-}$ while bixanthene is the sole product from $\mathbf{Fe^{III}(Hbim)}$ (cf. Eq. (5)). Reactions with [(phen)$_2$Mn(μ-O)$_2$(phen)$_2$]$^{3+}$ give both products [14,19,20]. 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 R$^{\bullet}$ to all three oxidants should be quite favorable with similar thermochemistry.

(10)

(11)
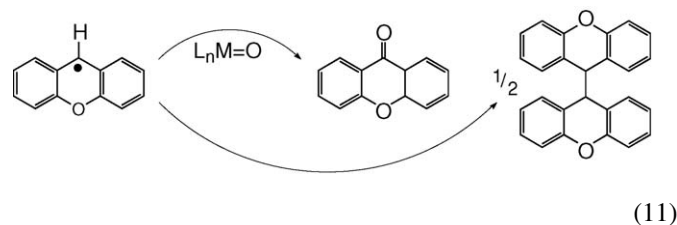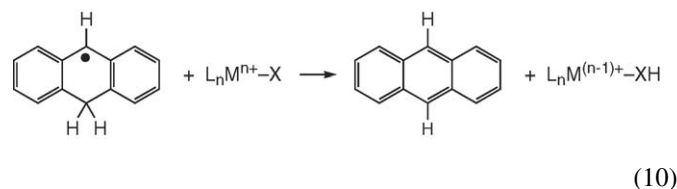
The addition of radical traps to C−H bond oxidation reactions can redirect the products and can provide additional evidence for the intermediacy of free-radicals. Typically, only oxidative radical traps can be used because reductive and unsaturated traps such as ^{n}Bu$_3$SnH, hydroquinone, BHT (2,6-^{t}Bu$_2$-4-MeC$_6$H$_2$OH) and alkenes are usually more reactive with the oxidant than even a weak C−H bond. CBrCl$_3$ is an effective trap, for instance, converting cyclohexyl radical to C$_6$H$_{11}$Br with $k = 2 \times 10^7$ M^{-1} s^{-1} [12], although the CCl$_3^{\bullet}$ formed is reactive and can propagate radical chains. With any radical trap,

Scheme 1. Square scheme for H• addition.
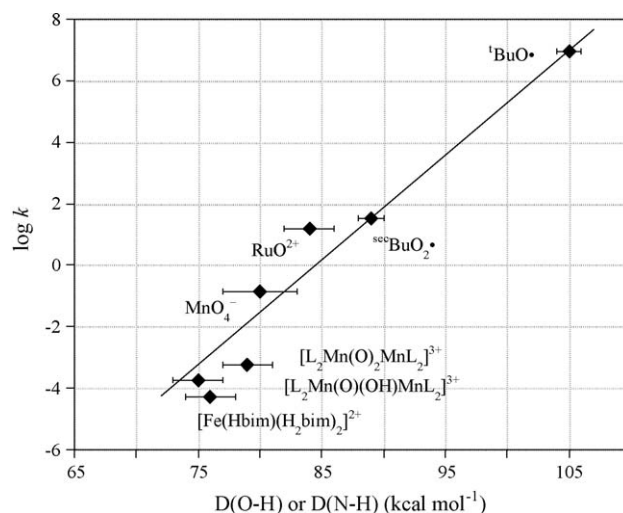

Fig. 2. Rate constants vs. thermochemical affinity for H• for hydrogen-atom transfer from 9,10-dihydroanthracene to various oxidants [25].

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 [32]. Dioxygen is an excellent radical probe because it reacts with carbon radicals at essentially diffusion limited rates, forming peroxyl radicals and various autoxidation products. Adding O_2 to a reaction implicates the intermediacy of carbon radicals when there are changes in the mixture of products and in the rate of disappearance of the oxidant, either faster or slower [14,20,25–27,33].

To understand why certain metal complexes can abstract H•, and to quantitatively understand the rate constants of such abstractions, the first parameter that should be considered is the thermochemical affinity of the oxidant for H•. This is directly analogous to needing the redox potential for analysis of an ET reaction. Bond dissociation enthalpies for C−H bonds are well known for small molecules [29,34] and many values for larger molecules have been reported, although assembling a complete and consistent set is often difficult. For metal reagents, the affinity for H• is most easily obtained from redox potential and pK_a measurements [9]. Any reagent involved in the transfer of H^+ and e^- has two relevant redox potentials $E°$ (for the protonated and deprotonated species), and two pK_a 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).

$$(E°_{AH^+} - E°_A) = \left(\frac{2.3RT}{F}\right)\{pK_a(AH^+) - pK_a(AH)\} \quad (12)$$

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 K_a are free energies so this cycle gives the bond dissociation free energy (BDFE) of AH, with $C = -23.06 E°(H^+)$ [35].

$$A + e^- \rightarrow A^- \qquad E°(A) \qquad (13)$$
$$A^- + H^+ \rightarrow AH \qquad -pK_a(AH) \qquad (14)$$
$$H^• \rightarrow e^- + H^+ \qquad C \qquad (15)$$

$$\overline{A + H^• \rightarrow AH \qquad\qquad\qquad (16)}$$

$$\Delta G°(AH \rightarrow A + H^•)$$
$$= -23.06 E°(A) + 1.37 pK_a(AH) + C$$
$$= -23.06 E°(AH^+) + 1.37 pK_a(AH^+) + C \quad (17)$$

Bordwell showed about 15 years ago that this approach could be used to determine a range of organic bond dissociation *enthalpies* (BDEs) [37] and we and others have used it to calculate solution BDEs for inorganic compounds [16,36,38,39]. BDEs are much more commonly used than BDFEs. In particular, the very extensive kinetic data on organic HAT reactions [40] has been understood in terms of BDEs and 'polar effects' [10,41]. Determining an enthalpy from the free energy measurements $E°$ and K_a requires a revised constant C to take into account the entropy of H• and requires the assumption that the entropies of A and AH are essentially equal. Recent work in our laboratory has shown the entropy assumption to be quite inaccurate for one class of compounds, as discussed elsewhere [9,42,43]. This work indicates that the correlations of rate with driving force should be done, where possible, with free energies instead of enthalpies [42,43].

The ability of a metal complex to abstract H• in most cases correlates very well with the thermochemistry calculated from Eqs. (13)–(17) [9,15]. The metal complex HAT rate constants also usually correlate well with the rate constants for oxyl radical reactions, within about two orders of magnitude in k (Fig. 2). In essence, metal complexes typically react as would be expected for an RO• species with a comparable affinity for H•. Thus, the relatively simple measurements of a redox potential and a pK_a predict, in most cases, the rate of HAT by a metal complex. An important conclusion from this work is that spin density is not an important predictor of HAT chemistry in a metal system: the reactivity of d^0, closed shell Mn^{VII} and Cr^{VI} compounds are comparable to or higher than paramagnetic Fe^{III} or Mn^{IV} centers [9].

The thermochemistry, however, is not the only parameter that affects the rate of HAT from AH to B. Organic chemists have long known, for instance, that oxyl radicals react much faster with O−H bonds than with C−H bonds, and the same reactivity pattern is observed in H-atom abstraction by metal complexes. Acetonitrile is remarkably unreactive with oxyl radicals despite its fairly weak C−H bonds of 94.8 ± 2.1 kcal mol^{-1} [29], with

$k \leq 10^2 \, \text{M}^{-1} \, \text{s}^{-1}$ for reaction with $^t\text{BuO}^\bullet$ [44]. Oxidizing metal complexes behave similarly, with acetonitrile being an excellent inert solvent. For instance, Que and co-workers have found that $[(\text{Bn-tpen})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ is unreactive with MeCN even though it oxidizes cyclohexane $[D(\text{C}-\text{H}) = 99 \, \text{kcal mol}^{-1}]$ [17]. This has been examined in a recent computational study [45]. The low reactivity of the hydrogen atoms in MeCN and other acidic ($\delta+$) C−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 C−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].

$$k_{XY} = \sqrt{k_{XX} k_{YY} K_{XY} f_{XY}} \tag{18}$$

Eq. (18) uses the free energy of reaction (in the form of the equilibrium constant K_{XY}) and the so-called self-exchange rate constants k_{XX} and k_{YY}, for the degenerate reactions such as $X + HX \rightarrow XH + X$ (f_{XY} is typically close to 1). The $\sim10^4$ faster reactions of O−H bonds versus C−H bonds of comparable strength are seen to trace from the $\sim10^8$ faster HAT self-exchange rate constants for O−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 $\text{A}^- + \text{HB}^+$ 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 (*p*-$\text{HO}_2\text{CC}_6\text{H}_4\text{CO}_2\text{H}$) predominantly by an HAT mechanism [49], related reactions of dimethylnaphthalenes are plagued
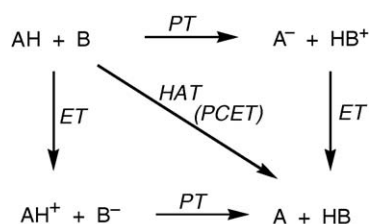
with side reactions, in part because the lower redox potential of the naphthalene leads to a competing ET pathway.

3. Oxidations of σ-bonds by OsO₄

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 tetroxide. 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 OsO₄-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 O_2 [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 an O−Os−O unit. Computational work from a number of laboratories support 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 RuO₄ and MnO_4^- with H_2; OsO₄ was reported not to react [57]. Based on computations and experiments (building on previous permanganate studies [58–61]), the H_2 reactions were concluded to occur by a [3 + 2] mechanism in which the H−H σ-bond is the "2" component.

We set out to determine whether the OsO₄ + 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, OsO₄ is readily reduced by H_2 in hexane, CHCl₃, or CCl₄ solution (Eq. (19)) [65].

$$\tag{19}$$
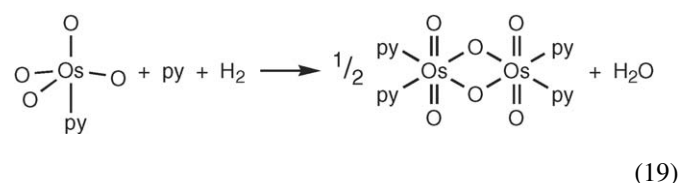
Under 1 bar H_2 in 24:1 CHCl₃/py, for instance, reduction is complete within 16 h at room temperature. In the absence of pyridine, there is no change in the optical spectrum of OsO₄ over 16 h in CHCl₃. The product is the well-known Os^{VI} dimer, Os₂O₆py₄ [66].

OsO₄ is also readily reduced by H_2 in aqueous solutions, forming osmate ($\text{OsO}_2(\text{OH})_4^{2-}$) at pH ≥ 8 (Eq. (20)). OsO₄

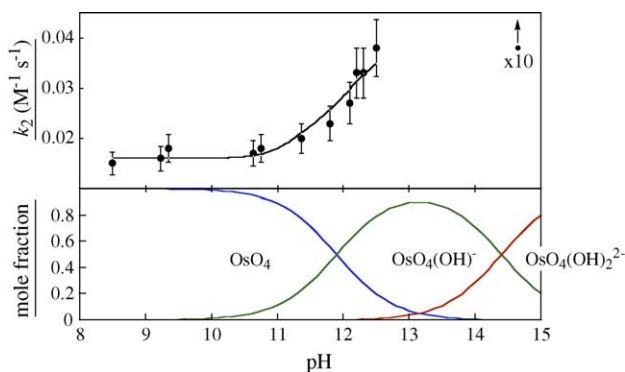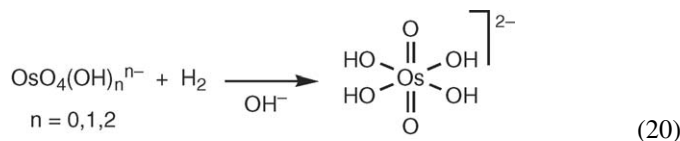Scheme 2. Square scheme for hydrogen-atom transfer.

Fig. 3. Top: plot of second order rate constants, k_2, vs. pH. The line represents the best fit to $-d[\text{Os}^{\text{VIII}}]/dt = [\text{H}_2]\{k_{\text{OsO}_4}[\text{OsO}_4] + k_{\text{OsO}_4\text{OH}^-}[\text{OsO}_4(\text{OH})^-]\}$. 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 Os$^{\text{VIII}}$. ©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.

$$\text{OsO}_4(\text{OH})_n^{n-} + \text{H}_2 \xrightarrow{\text{OH}^-} \left[\begin{array}{c} \text{HO} \quad \overset{\displaystyle O}{\underset{\displaystyle O}{\overset{\|}{\underset{\|}{\text{Os}}}}} \quad \text{OH} \\ \text{HO} \qquad\qquad \text{OH} \end{array} \right]^{2-}$$
$$n = 0,1,2 \tag{20}$$

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_{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 Os$^{\text{VIII}}$. Rate constants from 8 to 68 °C at pH 9.22 indicate $\Delta H^{\ddagger} = 13.2$ (2) kcal mol^{-1} and $\Delta S^{\ddagger} = -22.3$ (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)]$^-$ both contribute to the rate. The estimated rate constant for OsO$_4$ + H$_2$ in CHCl$_3$/py falls in between the aqueous k_{OsO_4} and $k_{\text{OsO}_4\text{OH}^-}$ [65].
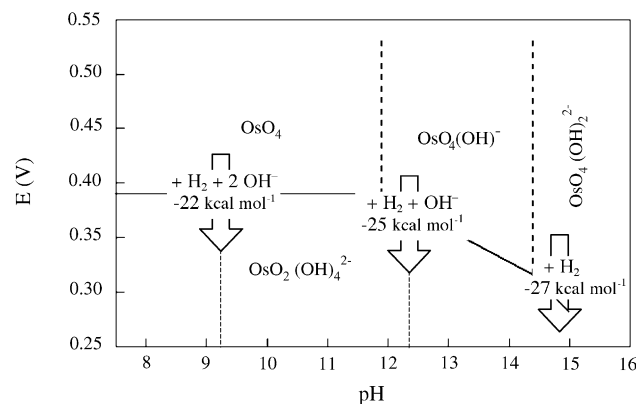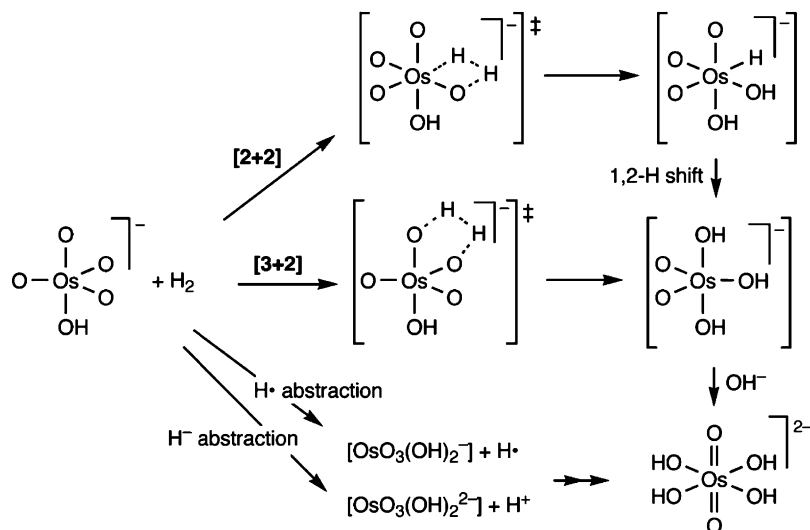

Fig. 4. Partial Pourbaix (*E*/pH) diagram for OsO$_4$ (1 M concentrations, *E* vs. NHE). ©American Chemical Society; reproduced with permission from [65].
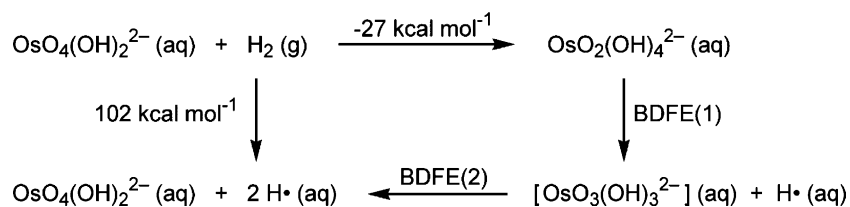
The free energy for the reduction of OsO$_4$(OH)$_n^{n-}$ with H$_2$ at a given pH is directly related to the redox potential at that pH, because aqueous redox potentials are referenced to the normal *hydrogen* electrode. The potentials are summarized in a Pourbaix diagram (Fig. 4) and the arrows give the ΔG° values for reaction with H$_2$ at pH 9.2, 12.3, and >14.2, respectively. (The "$\circ$" in ΔG° 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$_3$(OH)$^-$] + 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 Os$^{\text{VIII}}$).

Hydrogen-atom transfer, as discussed in the first half of this short review, depends on the bond dissociation free energies involved. The affinity of Os$^{\text{VIII}}$ species for H$^{\bullet}$ has not been

Scheme 3. Mechanisms for H$_2$ + OsO$_4$.

$$OsO_4(OH)_2{}^{2-} \text{ (aq)} + H_2 \text{ (g)} \xrightarrow{-27 \text{ kcal mol}^{-1}} OsO_2(OH)_4{}^{2-} \text{ (aq)}$$

$$102 \text{ kcal mol}^{-1} \downarrow \qquad\qquad\qquad\qquad \downarrow BDFE(1)$$

$$OsO_4(OH)_2{}^{2-} \text{ (aq)} + 2\,H\bullet \text{ (aq)} \xleftarrow{BDFE(2)} [OsO_3(OH)_3{}^{2-}] \text{ (aq)} + H\bullet \text{ (aq)}$$

Scheme 4. OsO—H 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 $\Delta G^\circ = -27\,\text{kcal mol}^{-1}$ for addition of H_2 to $OsO_4(OH)_2{}^{2-}$ implies that the sum of the two BDFEs is $129\,\text{kcal mol}^{-1}$ (Scheme 4). The putative Os^{VII} intermediate species being unstable to disproportionation means that $[Os^{VII}O_3(OH)_3{}^{2-}] + H\bullet \rightarrow Os^{VI}O_2(OH)_4{}^{2-}$ is more favorable than $Os^{VIII}O_4(OH)_2{}^{2-} + H\bullet \rightarrow [Os^{VII}O_3(OH)_3{}^{2-}]$. In other words, BDFE(1) must be larger than BDFE(2) [65]. This implies that BDFE(2) $< 65\,\text{kcal mol}^{-1}$ and therefore that $OsO_4(OH)_2{}^{2-} + H_2 \rightarrow [OsO_3(OH)_3{}^{2-}] + H\bullet$ has $\Delta G^\circ > 30\,\text{kcal mol}^{-1}$. This is larger than the observed $\Delta G^\ddagger$ of $20\,\text{kcal mol}^{-1}$, ruling out HAT for H_2 reduction of $OsO_4(OH)_2{}^{2-}$ and suggesting that neither OsO_4 nor $OsO_4(OH)^-$ react by this mechanism.

The $[2+2]$ and $[3+2]$ 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 $[3+2]$ pathway is much more favorable than the $[2+2]$ for alkene oxidation [54–56]. Calculations at the B3LYP level of density functional theory (DFT) for $H_2 + OsO_4$ shows the same strong preference for the $[3+2]$ mechanism, by $40\,\text{kcal mol}^{-1}$, respectively (Fig. 5) [65]. H_2 addition to $OsO_4(OH)^-$ is similar, with $\Delta H^\ddagger_{\text{calc}}(g) = +44.6$ and

$+10.6\,\text{kcal mol}^{-1}$ for the $[2+2]$ and $[3+2]$ 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 $\Delta H^\ddagger$ for $OsO_4 + H_2$ of $18.8\,\text{kcal mol}^{-1}$ is somewhat larger than the experimental aqueous $\Delta H^\ddagger = 13\,(2)\,\text{kcal mol}^{-1}$. Hydroxide binding lowers the barrier, computationally in the gas phase by $8\,\text{kcal mol}^{-1}$, experimentally in aqueous solution by less than $1\,\text{kcal mol}^{-1}$. H_2 addition to Os^{VIII} 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, $\Delta H^\circ_{\text{calc}}(g) = -51\,\text{kcal mol}^{-1}$ for $OsO_4(OH)^- + H_2 \rightarrow OsO_2(OH)_3{}^-$ while in water, $\Delta G^\circ = -27\,\text{kcal mol}^{-1}$ $OsO_4(OH)^- + H_2 + OH^- \rightarrow OsO_2(OH)_4{}^{2-}$.

The H—H bond in H_2 is comparable to or stronger than the C—H bonds in most hydrocarbons, so the facile oxidation of 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 C—H bonds (other than reports using peroxides which likely involve $RO\bullet$ [67,68]). RuO_4 oxidizes alkanes under fairly mild conditions and a $[3+2]$ mechanism has
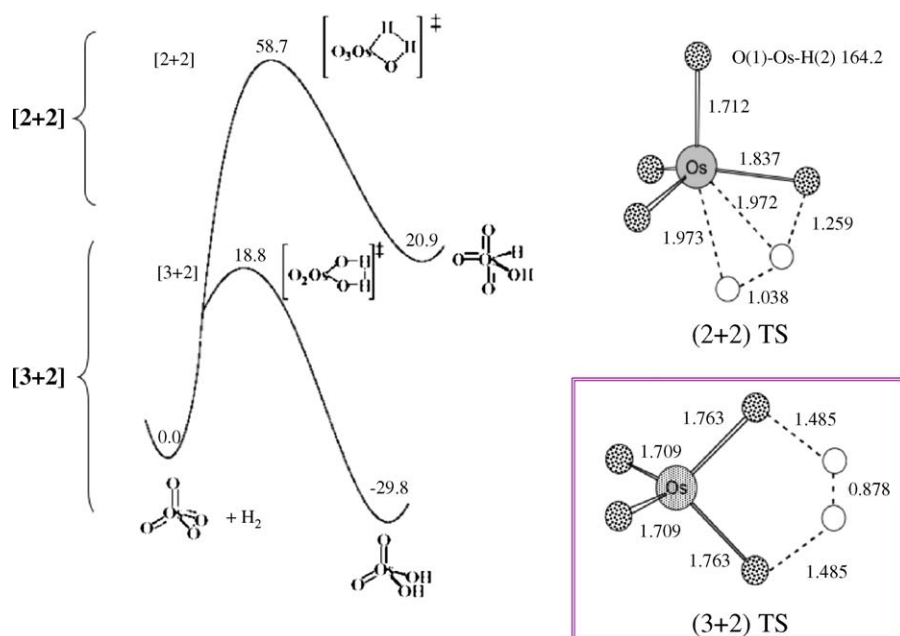
Fig. 5. Calculated enthalpies (kcal mol^{-1}) at 298 K for H_2 addition to OsO_4 by $[2+2]$ and $[3+2]$ mechanisms.

been suggested based on experiments [69–74] and very recently computations [75]. Our preliminary calculations for methane oxidation by OsO_4 suggest that barriers for C−H oxidations are higher than those for H_2, but not prohibitively so.

Aqueous solutions of OsO_4, set at pH of 12.1 with 0.30 M sodium phosphate buffer, react with 10 bar isobutane to give *t*-butanol over a week a 85 °C (Eq. (21)) [76]. ^tBuOH is formed in $30 \pm 3\%$ yield versus the starting OsO_4 concentration, essentially quantitative conversion based on the $30 \pm 1\%$ consumption of the initial Os(VIII) under these conditions. To measure the consumption of OsO_4, and to enable all measurements to be made by ^1H NMR, an assay was developed using the quantitative *cis*-dihydroxylation of styrene-4-sulfonate by aqueous Os(VIII) (Eq. (22)). Using 64 mM NaOH (pH 12.8) instead of phosphate buffer does not significantly affect the oxidation of isobutane. In the absence of organic substrate, there is ≤5% decay of Os(VIII) under these conditions.

$$(21)$$

$$(22)$$
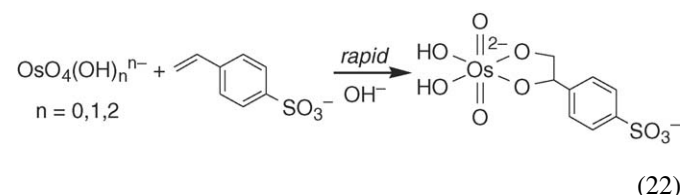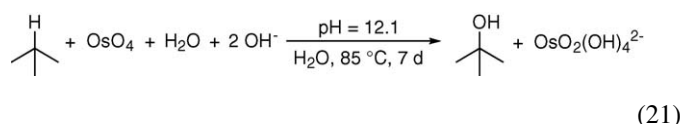
Oxidation of cyclohexane proceeds similarly at pH 12.1, yielding a mixture of adipate ($4.9 \pm 0.2\%$) and succinate ($1.8 \pm 0.20\%$) by ^1H NMR. While these yields per mole of OsO_4 are quite small, the oxidation stoichiometry requires 5 equivalents of $Os^{VIII} \rightarrow Os^{VI}$ for each adipate and 11 equivalents for each succinate (cyclohexane $\rightarrow$ succinate + $2CO_2$ is a 22-electron oxidation). As with isobutane, not all of the Os(VIII) is consumed in the reaction. Taking into account the stoichiometry and the $54 \pm 9\%$ consumption of OsO_4 in this experiment, the yields based on consumed oxidant are $46 \pm 2\%$ for adipate and

proceed via ene-diolate intermediates, $=C(O^-)_2$, which would be very rapidly oxidized by OsO_4. It is not clear why cyclohexane oxidation yield 6- and 4-carbon dicarboxylates but not the 5-carbon glutarate, and why cyclopentane does not yield the 4-carbon succinate.

Essentially all hydrocarbons with any water solubility have been observed to be oxidized by OsO_4 in basic solution at 85 °C. Toluene forms benzoate in $72 \pm 3\%$ yield based on OsO_4 consumed. Ethane is oxidized to acetate, which itself is slowly consumed. Propane forms only acetate, not propionate (which is persistent enough under these conditions that it would have been observed). Oxidation of propane likely occurs mostly at the secondary C−H bonds to give acetone, which is rapidly oxidized to acetate (probably via the enolate). Preliminary studies indicate that *cis*-9-decalinol is formed in low yield from *cis*-decalin (by GC/MS). Control experiments show that *trans*-9-decalinol would have been observed if it were formed, so this experiment suggests that hydroxylation is stereoselective. Related stereo-retentive hydroxylations of *cis*- and *trans*-decalins by RuO_4 were taken as evidence for a concerted [3 + 2] mechanism [69,71].

OsO_4 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), H_2O_2, and ferricyanide. For safety reasons, we have hesitated to heat gas mixtures of alkanes and O_2 in the presence of OsO_4. Our preliminary efforts at catalytic reactions have used periodate, IO_4^-. 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 OsO_4 and 170 mM $NaIO_4$ over 168 h at 85 °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 (Me_2CHCO_2H) 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 isobutylene and carbocation rearrangement (Eq. (24)).

Mechanistic studies of these alkane oxidations are ongoing.

$$(23)$$

$$(24)$$
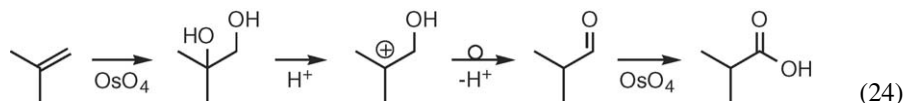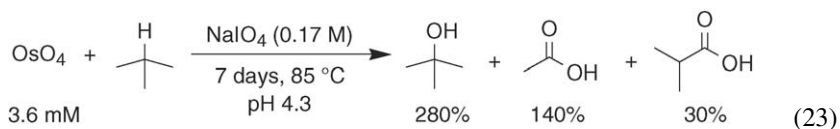
$37 \pm 7\%$ for succinate, so these products account for $83 \pm 7\%$ of the OsO_4 used. Under these conditions, adipate is observed to be oxidized to succinate, and succinate is slowly oxidized (presumably to CO_2).

Oxidation of cyclopentane gives a small amount of glutarate, $^-O_2C(CH_2)_3CO_2^-$, which is likely oxidized to malonate ($^-O_2CCH_2CO_2^-$) and then on to CO_2. These reactions may

It seems very unlikely that these are autoxidation reactions as no O_2 or peroxides are present in the initial reaction mixtures; the formation of O_2 from OsO_4 occurs only at very high pH. Hydroxyl radical is not the reactive oxidant based on the tertiary selectivity of isobutane oxidation: $OH^\bullet$ (aq) reacts competitively with the primary and tertiary C−H bonds of isobutane [77] and is quite reactive with ^tBuOH which is essentially inert

under our conditions. The thermochemistry discussed above suggests that $OsO_4(OH)_n^{n-}$ do not have sufficient affinity for $H^\bullet$ to abstract from cyclohexane, although parallel computational work is still 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, suggests that the reactions may be mechanistically more complex than a simple bimolecular reaction between an osmium species and the alkane. More studies are needed to determine whether these reactions are among the rare exceptions to the generalization 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 presence 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 driving force, as determined from the C−H bond strength and the thermochemical affinity of the metal complex for $H^\bullet$. 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 proceeds 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 hallmarks of a radical pathway but, given the prevalence of radical mechanisms, more studies are needed before this can be considered a firm conclusion.

Acknowledgments

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