Understanding C–H Bond Oxidations: H· and H^- Transfer in the Oxidation of Toluene by Permanganate

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The oxidation of toluene by permanganate has been studied as a model for the oxidation of C–H bonds by metal reagents, metalloenzymes, and metal oxide surfaces. In water, the reaction proceeds by hydride (H^-) transfer from toluene to a permanganate oxygen, whereas in toluene solution, permanganate abstracts a hydrogen atom (H·). The ability of permanganate to abstract a hydrogen atom is rationalized on the basis of the strong O–H bond formed on H· addition to permanganate. This approach allows understanding and prediction of the rates of hydrogen atom transfer from substrates to metal active sites.

The selective oxidation of C–H bonds by metal-oxo and related species is of fundamental and technological importance, from biological to industrial chemistry. A variety of metalloenzymes catalyze selective C–H bond oxidation reactions (*1*), and industrial oxidation reactions often use metal oxide surfaces as catalysts (*2*). Laboratory-scale syntheses of organic chemicals have utilized metal-oxo reagents such as permanganate (MnO_4^-) for more than a century (*3*). Surprisingly, these areas of oxidation chemistry have developed independently, and there is little understanding of the fundamental chemical principles that must underlie them all. There is particularly little insight into the features of an oxidant that enable it to activate a C–H bond. Described here is a mechanistic study of a textbook case, the oxidation of toluene by MnO_4^-. This reaction proceeds by different pathways in aqueous and organic solvents. The mechanism for the reaction in organic solvent is used to develop a paradigm for oxidation processes that involve hydrogen atom (H·) transfer from a substrate to a metal active site, based on the strength of the O–H bond formed at the active site and the well-known correlation of radical reaction rates with driving force. The paradigm provides qualitative and quantitative understanding of such H· transfer oxidations.

The reaction of $KMnO_4$ with toluene in aqueous buffer solutions forms colloidal MnO_2, as indicated by its characteristic optical spectrum [absorbance $A \propto \lambda^{-4}$ for wavelengths $\lambda > 625$ nm (*4*) (Fig. 1)] and by iodometric titration (average oxidation state 4.10 ± 0.09). The organic products, determined by high-performance liquid chromatography (HPLC), are benzoic acid (42.3 ± 2.7%) and benzaldehyde (0.6 ± 0.2%), in agreement with previous work (*5*) (yields are moles of product per mole of MnO_4^-). The observed products account for 85% of the oxidizing equivalents of MnO_4^- consumed in the reaction; the remainder are likely involved in the oxidation of the aromatic ring (*5*, *6*). The MnO_4^- solutions are stable in aqueous buffer in the absence of toluene.

The kinetics of toluene oxidation have been followed by ultraviolet-visible (UV-vis) spectroscopy (Fig. 1) under pseudo–first-order conditions of excess toluene. This could be accomplished despite the limited solubility of toluene in water because of the high absorptivity of MnO_4^-. A special cell was designed to enable anaerobic addition of a concentrated stock solution of MnO_4^- to an equilibrated toluene-water solution with essentially no vapor phase volume, to ensure that the toluene is in solution rather than in the gas phase (*6*). The disappearance of MnO_4^- follows first-order kinetics to greater than three half-lives with no induction period. The derived pseudo–first-order rate constant k_{obs} depends linearly on the toluene concentration and is independent of the initial permanganate concentration $[MnO_4^-]$, indicating the second-order rate law $d[MnO_4^-]/dt = -k_2[MnO_4^-][C_7H_8]$. At 293 K, $k_2 = 7.0 \times 10^{-4}\ M^{-1}\ s^{-1}$. An Eyring plot of rate constants determined over the temperature range 293 to 368 K gives an activation enthalpy $\Delta H‡ = 12.7 \pm 0.2$ kcal mol^{-1} and an activation entropy $\Delta S‡ = -30 \pm 1$ cal $mol^{-1}\ K^{-1}$ (Table 1).

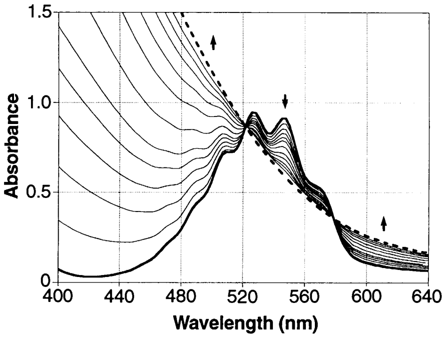
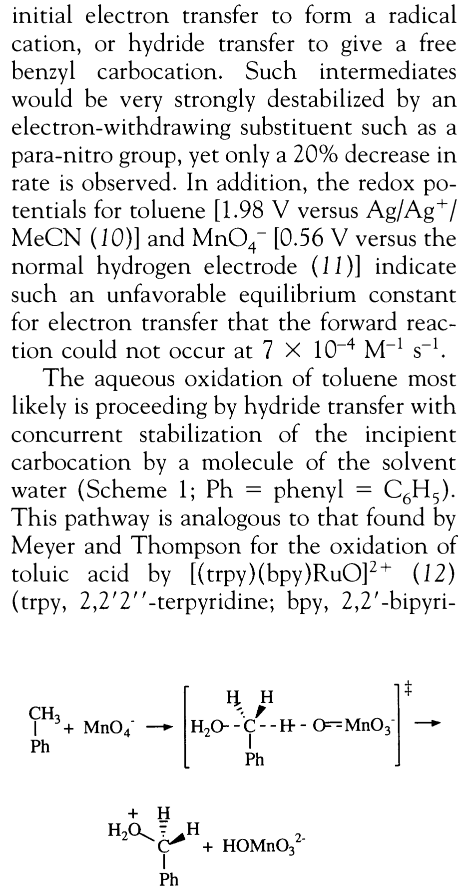


Fig. 1. Overlay of UV-vis spectra from the oxidation of toluene (6.9 mM) by potassium permanganate (0.392 mM) in pH 7.1 buffered aqueous solution at 75°C. The solid line is the initial permanganate spectrum and the dashed line is the final spectrum due to colloidal manganese dioxide.

The second-order rate law indicates that the reaction proceeds by attack on toluene by MnO_4^-, rather than involving intermediate species of some sort [as has been suggested (*3*)]. Consistent with this proposal, the rate constant is independent of ionic strength, pH (over the range 6 to 11), buffer type (phosphate and carbonate), and isotopic substitution of the solvent (H_2O versus D_2O). A substantial primary isotope effect is observed in the reaction of d_8-toluene: $k_{C_7H_8}/k_{C_7D_8} = 9.7$ at 293 K. The rate constant is the same for reactions performed under nitrogen and in oxygen-saturated water, under conditions where $[O_2] > [MnO_4^-]$. This finding implies that the reaction does not involve free radicals, as these would be intercepted by O_2, which traps radicals at rates near the diffusion limit (*7*). [MnO_4^- is also a highly effective radical trap (*8*).]

The relative rates of oxidation of the five para-substituted toluenes $CH_3C_6H_4X$, where X is CH_3, NO_2, COO^-, Cl, or SO_3^-, show a very small dependence of rate constant on substituent [a Hammett ρ value of −0.2 versus σ^+ (*6*, *9*)]. These data rule out initial electron transfer to form a radical cation, or hydride transfer to give a free benzyl carbocation. Such intermediates would be very strongly destabilized by an electron-withdrawing substituent such as a para-nitro group, yet only a 20% decrease in rate is observed. In addition, the redox potentials for toluene [1.98 V versus Ag/Ag^+/MeCN (*10*)] and MnO_4^- [0.56 V versus the normal hydrogen electrode (*11*)] indicate such an unfavorable equilibrium constant for electron transfer that the forward reaction could not occur at $7 \times 10^{-4}\ M^{-1}\ s^{-1}$.

The aqueous oxidation of toluene most likely is proceeding by hydride transfer with concurrent stabilization of the incipient carbocation by a molecule of the solvent water (Scheme 1; Ph = phenyl = C_6H_5). This pathway is analogous to that found by Meyer and Thompson for the oxidation of toluic acid by $[(trpy)(bpy)RuO]^{2+}$ (*12*) (trpy, 2,2′2″-terpyridine; bpy, 2,2′-bipyri-



Scheme 1.

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Table 1. Summary of kinetic data for the oxidation of toluene by permanganate.

Reaction	k_2 at 20°C (M^{-1} s^{-1})	ΔH‡ (kcal mol^{-1})	$S‡$ (cal mol^{-1} K^{-1})	k_H/k_D	Addition of O_2
Toluene + $KMnO_4$ in water	7.00×10^{-4}	12.7	−30	9.7 (at 20°C)	No effect on rate constant
Toluene + $^nBu_4NMnO_4$ in neat toluene	5.31×10^{-7}	21.0	−16	2.5 (at 45°C)	Significant increase in rate constant

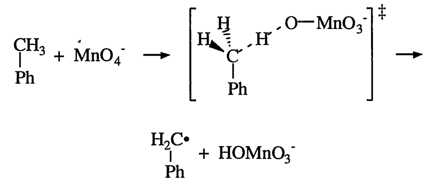
dine). Hydride abstraction by MnO_4^- is well established, for instance, in oxidations of alkoxide and formate ions (3). The quite ordered transition state is consistent with the large negative entropy of activation (−30 cal mol^{-1} K^{-1}), and the small $\Delta H‡$ is reasonable because bond formation accompanies bond cleavage. The mechanism is consistent with the Hammett study because water addition is concurrent with hydride loss, resembling an S_N2 pathway, so the benzylic carbon develops little carbocation character. An alternative mechanism involving [2+2] addition of a C–H bond across a Mn=O bond, recently suggested for a manganate oxidation (*13*), is unlikely on the basis of the solvent dependence, the difficulty of expanding the coordination sphere of MnO_4^-, and reactions of related substrates (*6*).

The oxidation of toluene by MnO_4^- has also been examined in toluene solvent, where there is no nucleophile like water to stabilize an incipient carbocation as in Scheme 1. The compound $^nBu_4N^+MnO_4^-$ (^nBu = $CH_3CH_2CH_2CH_2$) is used as an organic-soluble MnO_4^- salt (*14*). There are a few earlier reports of C–H bond oxidations by MnO_4^- in nonpolar solvents (*15*), but mechanistic studies were not performed. As in water, the products are colloidal MnO_2 [average oxidation state 4.05 ± 0.08 (*16*)] and primarily benzoic acid (31% based on MnO_4^-). The observed products account for 62% of the oxidizing equivalents of MnO_4^- consumed; the remainder may be used in toluene ring oxidation or in oxidation of the counterion, $^nBu_4N^+$.

First-order plots of UV-vis kinetic data in toluene solution (ln[MnO_4^-] versus time) show no induction period and are linear or show a slight downward curvature; quantitative values are typically derived from the initial rates. At 298 K, the first-order plot is linear to three half-lives with $k_{obs} = 7.74 \times 10^{-6}$ s^{-1}. This corresponds to a second-order rate constant of 8.26×10^{-7} M^{-1} s^{-1}, assuming a first-order dependence on toluene concentration, by analogy with related reactions of ethylbenzene and cumene (*6*). The oxidation in neat toluene is more than 1000 times slower than the reaction in water (Table 1). Activation parameters $\Delta H‡ = 21.0 \pm 1.0$ kcal mol^{-1} and $\Delta S‡ = -16 \pm 3$ cal mol^{-1} K^{-1} are derived from rate constants determined over the range from 298 to 338 K. An isotope effect of ~2.5 ($k_{C_7H_8}/k_{C_7D_8}$) is found at 318 K.

On the basis of the simple rate expression and the primary isotope effect, the rate-limiting step of the oxidation in neat toluene is attack of MnO_4^- to cleave the benzylic C–H bond, as in the aqueous reactions. However, the nature of this bond cleavage is different in the two solvents. A polar mechanism such as Scheme 1 is disfavored in toluene because of the difficulty of generating charged species in a nonpolar solvent and because of the absence of nucleophiles. Different mechanisms in the two solvents are also indicated by the very different rates, isotope effects, and activation parameters (Table 1). Most telling is that in neat toluene, the disappearance of MnO_4^- is about five times faster when the solution is saturated with O_2 (1 atm) and no longer follows first-order kinetics, indicating the intermediacy of benzylic radicals.

Oxidation in neat toluene most likely occurs by H· transfer from toluene to MnO_4^- (Scheme 2). There is strong evidence for organic radical intermediates in a number of MnO_4^- reactions (*3*), and similar mechanisms have been proposed for the MnO_4^- oxidations of substrates with tertiary C–H bonds (*17*). Closely related CrO_2Cl_2 oxidations of toluene, cyclohexane, cyclooctane, and isobutane proceed by initial H· transfer in nonpolar media (*18*, *19*). A H· transfer mechanism is also indicated by the correlation of the rate of oxidation with C–H bond strength in the reactions of toluene, ethylbenzene, and cumene (*6*). An alternative pathway involving formation of a Mn–C bond (*13*) is unlikely because it should be less facile with a tertiary substrate.



Scheme 2.

How can MnO_4^-, a closed-shell, diamagnetic species, abstract H· from toluene? Such H· abstraction is typically accomplished by radicals such as alkoxy or hydroxyl radicals, RO· and OH· [for a recent exception, see (*20*)]. The assumption that an active site with radical character is required for H· abstraction pervades the enzymatic and heterogeneous oxidation literature (*1*, *2*).

We propose that radical character in a metal oxidant is not required for H· abstraction (*18*, *19*). Rather, the ability of a species to abstract H· is the direct result of its thermodynamic affinity for a H·. The affinity of MnO_4^- for H· is the enthalpy ($\Delta H°$) for addition of H· to MnO_4^-, which is the O–H bond strength in $HMnO_4^-$. This enthalpy can be calculated by using the thermodynamic cycle in Scheme 3 (*6*, *18*). In essence, the affinity of MnO_4^- for H· is equivalent to its affinity for an electron (its redox potential $E°$) and a proton (the acid dissociation constant K_a of $HMnO_4^-$) because H· is equivalent to $H^+ + e^-$. An O–H bond strength of 83 kcal mol^{-1} is obtained after estimating the solvation of H· and the entropy of reaction [assuming that $S°(MnO_4^-) \cong S°(HMnO_4^-)$ (*6*, *18*)]. The same value is obtained from a thermodynamic analysis of Eq. 1 (HA = PhOH or $PhNH_2$).

$$MnO_4^- + HA \rightleftarrows HMnO_4^- + A\cdot \qquad (1)$$

The standard free energy $\Delta G°$ ($\cong \Delta H°$) can be calculated from the known $E°$ and K_a values (*21*), and the $\Delta H°$ is simply the difference between the $[O_3MnO{-}H]^-$ and H–A bond strengths. This procedure for calculating bond strengths to hydrogen has been developed and widely applied by Bordwell (*22*).

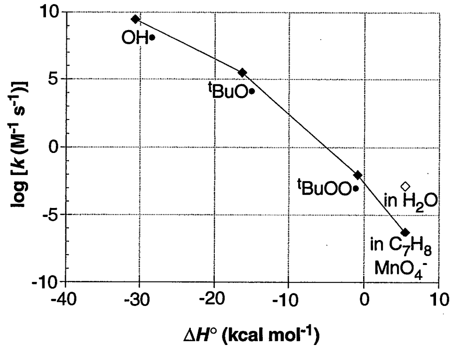


Fig. 2. Plot of the log of the rate constant *k* for hydrogen atom abstraction at 303 K versus $\Delta H°$ for hydrogen atom transfer [$D(PhCH_2{-}H) - D(RO{-}H)$]. The data for oxygen radicals is from (*24*).

$$\begin{array}{ll}
MnO_4^- + e^- \rightarrow MnO_4^{2-} & \\
\frac{1}{2}H_2 \rightarrow H^+ + e^- & E° = +0.564\ V \\
MnO_4^{2-} + H^+ \rightarrow HMnO_4^- & pK_a = 10.5 \\
H\cdot \rightarrow \frac{1}{2}H_2 & \text{Constant} = -56\ \text{kcal mol}^{-1} \\
\hline
MnO_4^{2-} + H\cdot \rightarrow HMnO_4^- & \Delta H° = -83\ \text{kcal mol}^{-1}
\end{array}$$

Scheme 3. Calculation of ΔH° for addition of H· to MnO_4^- (*18*). Constant = $\Delta H°\{H\cdot(g) \rightarrow \frac{1}{2}H_2(g)\} - \Delta H°\{H\cdot(g) \rightarrow H\cdot(aq)\} - \frac{1}{2}TS°\{H_2(g)\}$

The O–H bond strength of 83 kcal mol^{-1} in $HMnO_4^-$ is a critical value because it is well established that rates of radical reactions are directly related to bond strengths. For main-group radicals such as $(CH_3)CO\cdot$ ($^tBuO\cdot$), the Polanyi equation (*23*) states that the activation barrier for an H· transfer reaction, or log *k*, is proportional to the driving force, $\Delta H°$. The $\Delta H°$ for a H· transfer reaction $A–H + B \rightleftarrows A + H–B$ is simply the difference between the A–H and B–H bond strengths. An ·OH abstracts a benzylic hydrogen from toluene at an almost diffusion-limited rate because H· transfer is highly exothermic (31 kcal mol^{-1}), based on the bond dissociation energies $D(PhCH_2–H) = 88.5 \pm 1.5$ kcal mol^{-1} and $D(HO–H) = 119.3$ kcal mol^{-1} (*24*). Reactions of toluene with $^tBuO\cdot$ and especially $^tBuOO\cdot$ are slower because the reactions are less favorable, in the last case, downhill by only 1 kcal mol^{-1} [$D(^tBuO–H) = 104.8$ kcal mol^{-1}, $D(^tBuOO–H) = 89.4$ kcal mol^{-1} (*24*)].

A plot of the Polanyi relation, log *k* versus $\Delta H°$ for H· abstraction from toluene, is shown in Fig. 2. The rate of H· abstraction by MnO_4^- correlates with the rates of reaction of main-group radicals. In other words, MnO_4^- abstracts H· from toluene just as an oxygen radical would if it had a bond strength of 83 kcal mol^{-1}. This is true even though MnO_4^- is not a radical. Similar correlations have been found for oxidations of ethylbenzene by RO· and MnO_4^- (*6*) and for oxidations of toluene, cyclohexane, and isobutane by RO· and CrO_2Cl_2 [on the basis of an estimated CrO–H bond strength (*18*, *19*)]. The rate of toluene oxidation by MnO_4^- in water does not fit this relation because the mechanism is not H· abstraction; rates of H· transfer are essentially independent of solvent (*25*).

The correlation of rate with driving force provides insight into how a metal-containing active site can remove a hydrogen atom from an organic substrate. This correlation should apply not only to reagents such as permanganate but also to active sites in metalloenzymes and on metal oxide surfaces. The key feature of such an active site is not its radical character but its affinity for H·. Understanding these reactions should be based primarily on the thermochemistry of the H· abstraction step.

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Global Distribution of Persistent Organochlorine Compounds

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The global distribution of 22 potentially harmful organochlorine compounds was investigated in more than 200 tree bark samples from 90 sites worldwide. High concentrations of organochlorines were found not only in some developing countries but also in industrialized countries, which continue to be highly contaminated even though the use of many of these compounds is restricted. The distribution of relatively volatile organochlorine compounds (such as hexachlorobenzene) is dependent on latitude and demonstrates the global distillation effect, whereas less volatile organochlorine compounds (such as endosulfan) are not as effectively distilled and tend to remain in the region of use.

Researchers have long speculated that some organic pollutants move through the atmosphere from relatively warm source regions and condense at colder, higher latitudes onto vegetation, soil, and bodies of water. This process, known as the global distillation effect, could be the cause of the high concentrations of some pollutants found in Earth's arctic regions (*1–5*). Global distillation is driven by the change of a pollutant's subcooled liquid vapor pressure with temperature, its environmental persistence, and its tendency to associate with lipids (*1*, *6*). This effect appears to be most pronounced for organochlorine compounds of intermediate volatility, many of which are used as insecticides and fungicides. Some of these compounds are still in use throughout the world (for example, endosulfan), whereas others have been banned in almost all developed countries (for example, DDT). Understanding the environmental fate of these compounds is particularly important because some of them are carcinogens and some may be estrogen mimics (*7*).

These ubiquitous organochlorine pollutants have subcooled liquid vapor pressures of 0.1 to 0.001 Pa at 25°C (*8*). Although these vapor pressures are sufficient for all of

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