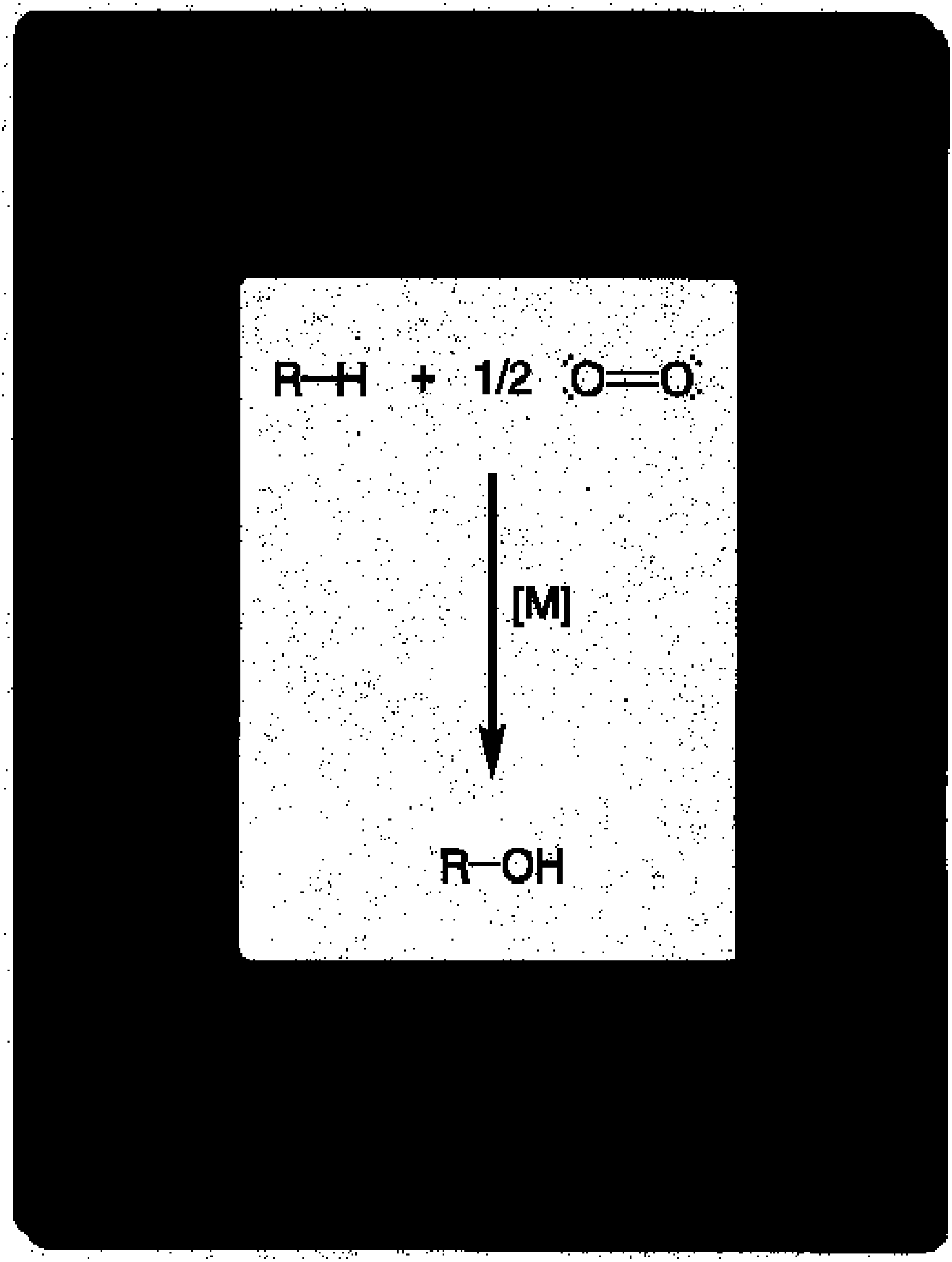
Alkane oxidation by late transition metals



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Homogeneous Oxidation of Alkanes by Electrophilic Late Transition Metals

Shannon S. Stahl,* Jay A. Labinger, and John E. Bercaw

Despite being the most abundant and least expensive hydrocarbon feedstocks available, alkanes find limited use as a starting material for the chemical industry. Unfortunately, few methods exist for the selective conversion of alkanes into more valuable products. Although alkanes are relatively unreactive (e.g., high ionization energies and pK_a values, low electron affinity), the main challenge facing alkane transformations is selectivity, not reactivity. Surface-catalyzed methods as well as many radical reactions often lead to overoxidation of the alkane to CO_2 and H_2O. In contrast, many organometallic complexes in homogeneous solutions undergo reaction with alkanes with unprecedented selectivity. Unfortunately, most of these systems are not amenable to catalytic transformations, since the reactive organometallic species is typically extremely sensitive to stoichiometric oxidants which might be used in the reaction. Recently, considerable attention has been directed toward the catalytic oxidation of alkanes in homogenous solutions using electrophilic late transition metal ions (e.g., Pt^{II}, Pd^{II}, and Hg^{II}). Such systems are remarkably robust (the reactions are often carried out in aqueous or strong acid solvents in the presence of O_2) and exhibit the unusual selectivity patterns characteristic of organometallic reagents. Such reactions offer a potentially practical approach for the selective transformation of alkanes. This review will survey recent discoveries of new catalytic systems as well as advances in the mechanistic understanding of such reactions.

Keywords: homogeneous catalysis ·

1. Introduction

Economic factors and technological innovations often induce changes in the chemical feedstocks used to produce commodity organic chemicals. These reasons caused olefins to replace acetylene in many commercial processes several decades ago. Alkanes, however, are the least expensive and most abundant hydrocarbon resource and thus represent an important potential feedstock for the chemical industry. Unfortunately, very few selective methods are available for converting alkanes into more valuable products. Furthermore, several desirable reactions utilizing alkanes are not thermodynamically favorable at reasonable temperatures. Even where alkanes are used, their transformations are often inefficient. For example, alkanes are used in the generation of synthesis gas [CO + H_2, "syngas"; Eq. (1)] by the "steam reforming" of methane, the primary component of natural gas. Syngas may then be used directly in industrial reactions (e.g., hydroformylation of olefins), but it is often converted into methanol for use as a fuel or as a chemical feedstock [Eq. (2)]. The direct oxidation of methane represents a much more efficient pathway for methanol synthesis [Eq. (3)].

$$CH_4(g) + H_2O(g) \xrightarrow{[Ni],\ \Delta} CO(g) + 3\,H_2(g) \qquad \Delta H^\circ = 49.3\ \text{kcal mol}^{-1} \tag{1}$$

$$CO(g) + 2\,H_2(g) \xrightarrow{[Cu/ZnO]} CH_3OH(g) \qquad \Delta H^\circ = -21.7\ \text{kcal mol}^{-1} \tag{2}$$

$$CH_4(g) + 1/2\,O_2(g) \longrightarrow CH_3OH(l) \qquad \Delta H^\circ = -30.7\ \text{kcal mol}^{-1} \tag{3}$$

Attempts to selectively oxidize alkanes encounter two important problems. First, with respect to chemoselectivity, the initial product of alkane oxidation is often more reactive toward the oxidant than the alkane itself. For example, the C–H bond in methanol is 11 kcal mol^{-1} weaker than that in methane (93 and 104 kcal mol^{-1}, respectively). Consequently, if methane oxidation involves the abstraction of a hydrogen atom, the rate of which is usually governed by C–H bond strength, overoxidation of methanol (ultimately leading to CO_2) will dramatically reduce the desired product yield.[1] The

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regioselectivity of alkane oxidation is also problematic. In reactions with alkanes, both radical and electrophilic (i.e., superacid) reagents preferentially attack tertiary over primary and secondary C–H bonds (3° > 2° > 1°).[2, 3] However, the selectivity is often not high, and the desired preference is usually in the opposite direction.

Recent work suggests that homogeneous organometallic systems can overcome some of these selectivity problems.[4–10] Indeed, the many examples of "organometallic"[11] alkane activations suggest that a reversed regioselectivity pattern can be attained (i.e., 1° > 2° > 3°). Further, strong C–H bonds can be activated selectively in the presence of weaker C–H bonds (e.g., aromatic C–H bonds are activated before benzylic C–H bonds in toluene).[12] Several approaches to organometallic activation reactions are shown in Figure 1.[4–9] Despite the success in this area, few systems are capable of subsequent substrate functionalization and regeneration of the metal fragment as required for catalytic turnover. In most cases the reactive metal species responsible for alkane activation is incompatible with oxidants (e.g., O_2, H_2O_2) required for catalysis.

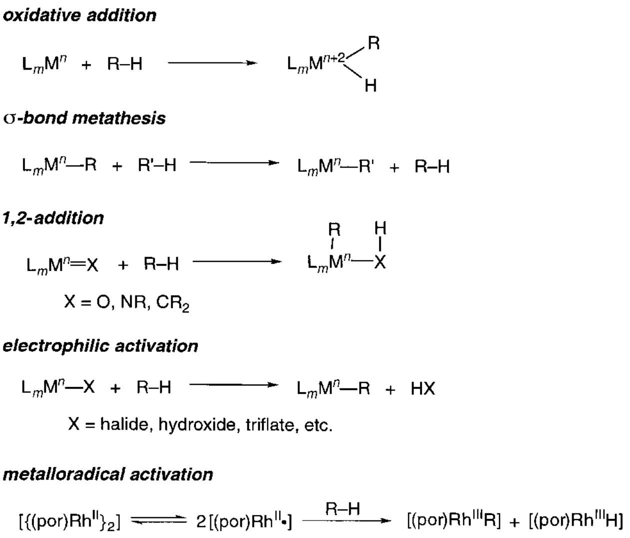

Figure 1. Various pathways discovered for the activation of alkane C–H bonds. In the reactions the stoichiometry, but not necessarily the mechanism, is specified. por = porphyrin.

An important exception to this limitation is the reaction of alkanes with chloroplatinum salts in aqueous solution. Ironically, this system is one of the earliest examples of C–H activation. In 1969 Shilov and co-workers observed the incorporation of deuterium into alkanes in solutions of $K_2[PtCl_4]$ in D_2O/[D_1]acetic acid.[13] Three years later the same group reported that addition of $H_2[PtCl_6]$ to the reaction mixture generated oxidized alkane products [RCl and ROH; Eq. (4)].[14] This system is remarkably robust; unlike the organometallic reagents shown in Figure 1, which are extremely air- and moisture-sensitive, the platinum complexes are soluble in water, and the reactions are unaffected by the

$$CH_4 + [PtCl_6]^{2-} + H_2O\ (Cl^-) \xrightarrow[H_2O,\ 120^\circ C]{[PtCl_4]^{2-}} CH_3OH\ (CH_3Cl) + [PtCl_4]^{2-} + 2\ HCl \quad (4)$$

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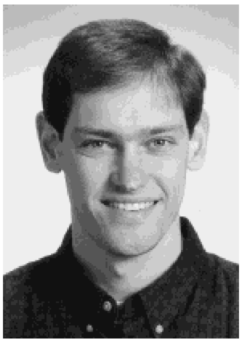
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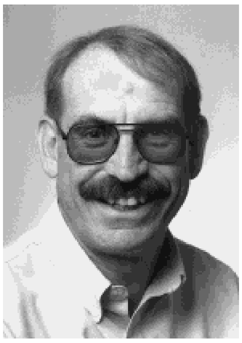
J. E. Bercaw

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John E. Bercaw, born in 1944, studied at North Carolina State University, received his Ph.D. in 1971 at the University of Michigan under the direction of H. Brintzinger, and carried out postdoctoral research at the University of Chicago with J. Halpern. In 1972 he moved to the California Institute of Technology as the A. A. Noyes Research Fellow in Chemistry and is now the Centennial Professor of Chemistry.

presence of O_2. The doubly solvated complex $[PtCl_2(H_2O)_2]$ has been proposed as the active catalytic species, and the observed selectivity patterns reflect those of other organometallic activation systems, namely, 1° > 2° > 3°.[8]

In recent years, several new alkane oxidations have been discovered that utilize electrophilic late transition metals in strongly acidic media (e.g., CF_3CO_2H, H_2SO_4).[15–33] These systems exhibit significant similarities to the platinum chemistry discussed above, and together they represent an extremely promising approach to alkane functionalization. They not only offer new insights into factors necessary for selective conversion of alkanes, but also have potentially practical utility. This review will survey recent studies exploring the scope, selectivity, and mechanism for platinum(II)-catalyzed alkane oxidations in aqueous solvents,[34] and will summarize related homogeneous oxidation reactions involving other late transition metals in strong acid solvents.

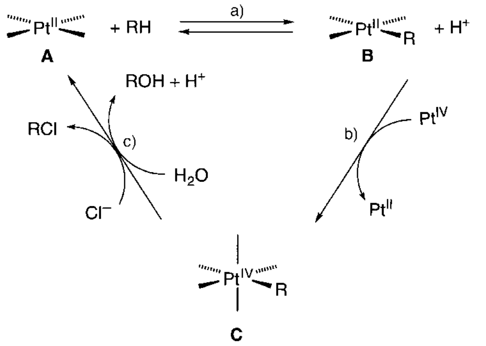
Biological and related biomimetic systems (e.g., methane monooxygenase, Gif) represent important complementary approaches to alkane oxidation. These often involve the metal-catalyzed activation of O_2 to generate an intermediate that reacts directly with alkanes. While these topics are beyond the scope of the present article, several recent reviews and monographs are recommended.[35–41]

2. Alkane Oxidation by Platinum Complexes in Aqueous Solution

2.1. Mechanistic Studies

2.1.1. Proposed Mechanism

In 1983 Shilov et al. proposed a mechanism for platinum-catalyzed alkane oxidation consisting of three basic transformations (Scheme 1):[42] a) activation of the alkane by Pt^{II} to generate an alkylplatinum(II) intermediate, b) two-electron oxidation of the alkylplatinum(II) intermediate to generate an alkylplatinum(IV) species, and c) reductive elimination of RX (X = Cl or OH) to liberate the oxidized alkane and the Pt^{II} catalyst. This proposal has received considerable attention from several research groups. While the general catalytic cycle shown in Scheme 1 was quickly accepted, many features of the individual steps have only recently been identified. Each of the three steps in Scheme 1 can potentially proceed by (at least) two different pathways. These possibilities and the experiments used to distinguish between them are discussed in the following section. The steps of the catalytic cycle will be discussed in reverse order, according to the chronology of their elucidation.



Scheme 1. Proposed catalytic cycle for the platinum-catalyzed oxidation of alkanes in aqueous solution.

2.1.2. Reductive Elimination of ROH/RCl from Platinum(IV)

Alkane functionalization is completed by reductive elimination of RX from a platinum(IV) complex (step (c) in Scheme 1). Two different mechanisms have been postulated for this reaction: a nucleophilic (S_N2) pathway (**D**, Figure 2) and a concerted reaction via a three-center transition state (**E**). Zamashchikov and co-workers were the first to examine this step directly. They prepared the alkylplatinum(IV) intermediate $[Pt(R)Cl_5]^{2-}$ (**1**) (R = CH_3, CH_2CH_3, CH_2COCH_3, etc.) independently and monitored the kinetics of its decomposition in aqueous solutions to form RCl and ROH.[43–50] As described below, these and additional studies by Luinstra et al.[51, 52] definitively establish that R–X bond formation proceeds by an S_N2 mechanism.

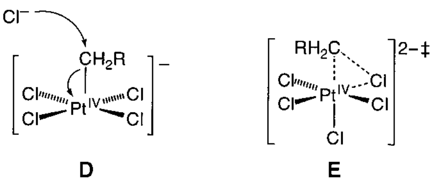
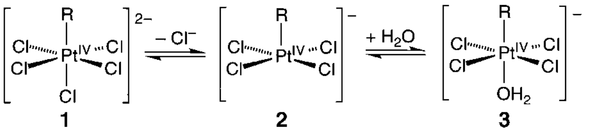


Figure 2. Two possible pathways for reductive elimination of RCH_2Cl from a platinum(IV) complex: S_N2 (**D**) and a concerted mechanism via a three-center transition state (**E**).



(5)

Various alkylplatinum(IV) complexes are most readily prepared by oxidative addition of RI to $[PtCl_4]^{2-}$, although they also have been reported to form under certain conditions by oxidation of RH in aqueous solutions of $[PtCl_4]^{2-}/[PtCl_6]^{2-}$ (i. e., generated by steps (a) and (b) in Scheme 1).[42, 53] These complexes exist in equilibrium with their monoaquo derivatives (**3**) in aqueous solution [Eq. (5)]. Complex **2** is presumed to be an intermediate in this equilibrium. The equilibrium constant K for $\mathbf{1} \rightleftharpoons \mathbf{3}$ when R = methyl is about 0.8 M [Eq. (6)].[44, 51, 52] The rate expression for the formation of RCl shown in Equation (7) was obtained by monitoring the

$$K = \frac{[\mathbf{3}][Cl^-]}{[\mathbf{1}]} \qquad (6)$$

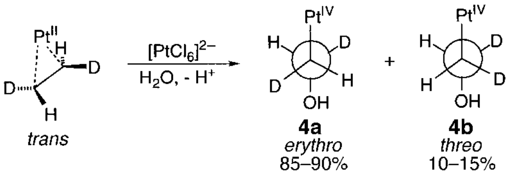
$$-\frac{d[\mathbf{1}+\mathbf{3}]}{dt} = k_{obs}[\mathbf{1}+\mathbf{3}]; \quad k_{obs} = \frac{k_1[Cl^-] + k_2[H_2O]}{1 + K^{-1}[Cl^-]} \qquad (7)$$

decay of the alkylplatinum(IV) complexes **1** and **3**. The kinetics cannot distinguish between nucleophilic attack on the aquo complex **3** or the proposed five-coordinate intermediate **2**;

however, the latter is favored since it represents the microscopic reverse of oxidative addition of methyl halide to square-planar d^8 complexes.

Evidence against a three-center, concerted pathway was obtained when monitoring the decomposition of **1** and **3** in the presence of other anions such as bromide and iodide. Under reaction conditions where these halides are not incorporated into the platinum coordination sphere *cis* to the alkyl group, formation of RX (X = Br, I) is observed in large preference to that of RCl.[47, 48] This result strongly supports R–X bond formation by external nucleophilic attack.

Perhaps the most definitive evidence favoring the S_N2 pathway for R–X bond formation is inversion of stereochemistry at the platinum-bound carbon center upon reductive elimination.[51, 52] (Concerted reductive elimination through a three-center transition state is expected to result in retention of configuration.) Formation of a platinum(IV) complex bearing a diastereomerically enriched alkyl group is obtained by oxidation of isotopically labeled Zeise's salt by $[PtCl_6]^{2-}$ (see Scheme 3 for the mechanism). Specifically, oxidation of Zeise's salt containing *trans*-dideuteroethylene yields predominantly ($\approx$ 85–90 %) the *erythro* β-hydroxyethyl product $[Pt(CHDCHDOH)Cl_5]^{2-}$ (**4a**). The *threo* isomer (**4b**) is also formed in 10–15 % [Eq. (8)]. Decomposition of **4** in the presence of chloride and subsequent conversion of the resulting 2-chloroethanol (**5**) into ethylene oxide (**6**) provides the *cis* isomer in isotopic purity identical to the initial alkylplatinum(IV) complex **4** [Eq. (9)]. This sequence clearly reflects inversion of stereochemistry in the reductive elimination reaction, which is consistent with an S_N2 mechanism.



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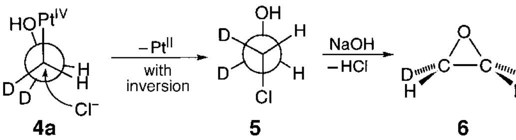
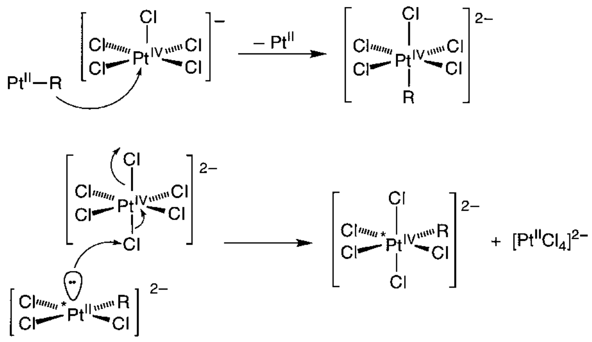


(9)

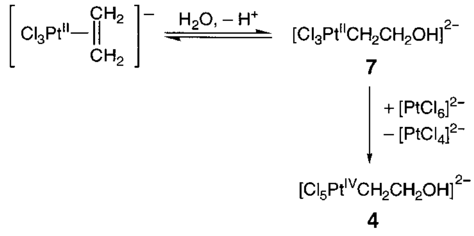
2.1.3. Oxidation of RPt^{II} to RPt^{IV}

Development of a practical method for alkane oxidation requires that the reaction be coupled to consumption of an inexpensive stoichiometric oxidant (preferably O_2). Platinum(IV) is clearly impractical as a stoichiometric oxidant! Two possible mechanisms have been considered for oxidation of the alkylplatinum(II) intermediate to platinum(IV) (step (b) in Scheme 1): 1) alkyl transfer from RPt^{II} to Pt^{IV} or 2) inner-sphere, two-electron transfer from RPt^{II} to Pt^{IV} (i.e., chloronium ion transfer; Scheme 2). Whereas the former demands the presence of platinum(IV) to produce the alkylplatinum(IV) intermediate, the latter is compatible with the use of less expensive oxidants. Importantly, recent studies support the second pathway, suggesting that practical alternatives to Pt^{IV} may be possible.[52, 54, 55]



Scheme 2. Two possible pathways for the oxidation of the alkylplatinum(II) intermediate by $[PtCl_6]^{2-}$.

Direct study of the oxidation step was delayed for many years because the alkylplatinum(II) intermediate (**B**, Scheme 1) could not be prepared. In protic solvents the methyl derivative rapidly undergoes protonolysis to liberate methane,[43, 52, 56] and in nonprotic media it disproportionates to $[Pt(CH_3)_2Cl_2]^{2-}$ and $[PtCl_4]^{2-}$.[55] Luinstra et al. circumvented this problem by examining the oxidation of Zeise's salt by $[PtCl_6]^{2-}$.[52, 54] Kinetic studies reveal that this reaction proceeds through a transient alkylplatinum(II) intermediate (**7**, Scheme 3). When isotopically labeled $Na_2[^{195}PtCl_6]$ was used, the ^1H NMR spectrum of the product **4** revealed ^{195}Pt satellites for the Pt-CH_2CH$_2$OH peak of normal intensity, that is, 33 % of the total peak area (natural abundance of $^{195}Pt \approx$ 33 %). Thus, no alkyl transfer occurs in this reaction.



Scheme 3. Oxidation of Zeise's salt by Pt^{IV}.

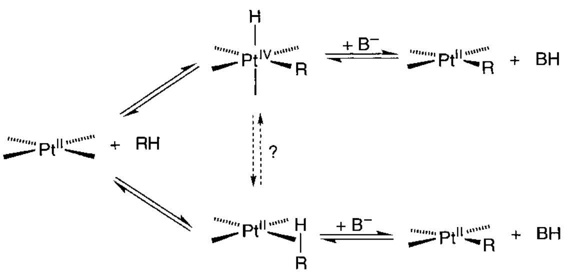
Recently, the methylplatinum(II) complex $[Pt(CH_3)Cl_3]^{2-}$ was prepared by reduction of $[Pt(CH_3)Cl_5]^{2-}$ by cobaltocene in THF.[55] Rapid precipitation of the product prevents the disproportionation reaction discussed above. Subsequent dissolution of $[Pt(CH_3)Cl_3]^{2-}$ in an aqueous solution containing $[^{195}PtCl_6]^{2-}$ [Eq. (10)] confirms the result obtained for the

$$[\mathrm{Pt^{II}(CH_3)Cl_3}]^{2-} + [^{195}\mathrm{PtCl_6}]^{2-} \xrightarrow{\mathrm{H_2O}} [\mathrm{Pt^{II}(CH_3)Cl_5}]^{2-} + [^{195}\mathrm{PtCl_4}]^{2-} \qquad (10)$$

oxidation of Zeise's salt: The reaction proceeds by electron transfer, not alkyl transfer.

2.1.4. Electrophilic Activation of Alkanes by Platinum(II)

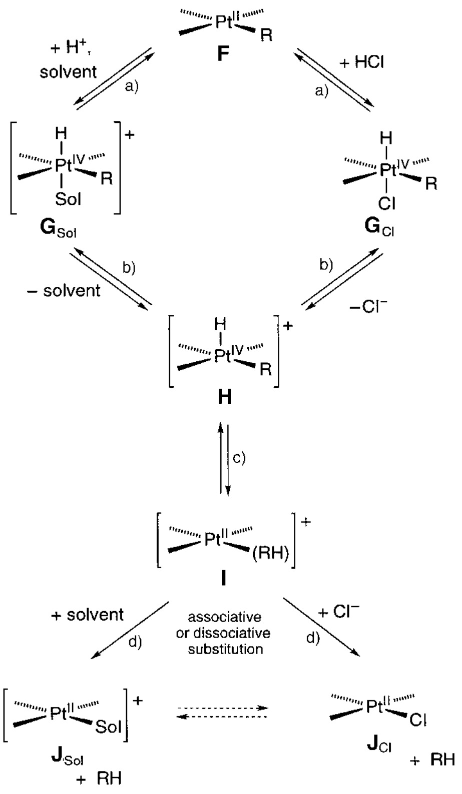
The C–H activation (step (a) in Scheme 1) appears to determine both the rate and selectivity of the alkane oxidation, thus providing significant motivation to understand the details of its mechanism. Unfortunately, this step has proven to be the most difficult to study. As indicated in Scheme 1, the reaction stoichiometry involves electrophilic displacement of a proton on the alkane by Pt^{II}. Once again two different mechanisms have been considered for this reaction (Scheme 4):[1, 8, 57–59] 1) oxidative addition of the C–H bond at Pt^{II} yielding an alkyl(hydrido)platinum(IV) complex which is subsequently deprotonated, or 2) deprotonation of an intermediate Pt^{II}–alkane σ adduct. In fact, considerable evidence has been obtained recently supporting the intermediacy of both species.[56, 60]



Scheme 4. Two possible pathways for alkane C–H activation by Pt^{II}: oxidative C–H addition and subsequent deprotonation of the Pt^{IV} hydride, or formation and subsequent deprotonation of an alkane σ adduct

Early studies of C–H activation focused on deuterium incorporation into protio alkanes in solutions of $[PtCl_4]^{2-}$ in D_2O.[8] While substantial evidence supports the homogeneity of these reactions, deposition of platinum metal often complicates detailed studies. Furthermore, the reaction conditions (>100 °C) for C–H activation are not expected to allow detection of reactive intermediates. Consequently, most of the mechanistic information for this reaction has been obtained by studying the microscopic reverse of this reaction, namely, protonolysis of alkylplatinum(II) complexes.

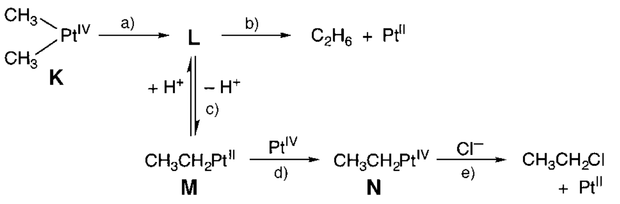
Characterization of the first alkyl(hydrido)platinum(IV) complexes has recently been reported for a series of model complexes with stabilizing nitrogen, phosphane, or tris(pyrazolylborate) ligands.[56, 60–68] Very recently, Wick and Goldberg reported that three-coordinate (see below) $[(\eta^2\text{-Tp}')Pt^{II}(CH_3)]$ (Tp′ = hydridotris(3,5-dimethylpyrazolyl)borate), generated in situ by treatment of $[(\eta^2\text{-Tp}')Pt^{II}(CH_3)_2]^-$ with $B(C_6F_5)_3$, reacts with a solvent molecule with cleavage of C–H bonds to afford stable dialkyl(hydrido)platinum(IV) complexes $[(\eta^3\text{-Tp}')Pt^{IV}(CH_3)(R)(H)]$ (R = *n*-pentyl, cyclohexyl).[69] Most alkyl(hydrido)platinum(IV) complexes are generated by addition of HX (X = halide, triflate, etc.) to the corresponding alkylplatinum(II) complexes at low temperatures. Furthermore, in deuterated acidic media, multiple H/D exchange into the alkyl positions is observed prior to elimination of the alkane for certain classes of these alkyl hydride complexes.[56, 60, 61, 66] The results from these studies support the mechanism shown in Scheme 5 for the protonolysis of alkylplatinum(II) complexes: a) chloride- or solvent-mediated protonation of Pt^{II} (**F**) to generate an alkyl(hydrido)platinum(IV) intermediate (**G**); b) dissociation of the solvent molecule or chloride to generate a cationic, five-coordinate platinum(IV) species (**H**); c) reductive C–H formation producing an alkane σ complex (**I**); and d) irreversible loss of alkane, either through an associative or dissociative substitution pathway. In the presence of D^+, deuterium incorporation into the alkyl group can be explained by the reversibility of steps (a)–(c). Extrapolation of these results to the Shilov system suggests that $[Pt^{IV}(R)(H)]$ and alkane σ adducts are intermediates in the C–H activation of alkanes by platinum(II). Importantly, however, formation of the alkylplatinum(II) intermediate (**B**, Scheme 1) arises from deprotonation of the $[Pt^{IV}(R)(H)]$ species **H**, not the σ adduct **I**.



Scheme 5. Proposed mechanism for the protonolysis of alkylplatinum(II) complexes, the microscopic reverse of C–H activation by Pt^{II}.

The relevance of Scheme 5 to the Shilov system is supported by related chemistry observed for alkylplatinum(II/IV) chloride complexes. Using conditions closely resembling those of alkane oxidation (95 °C, aqueous chloride solutions), Zamashchikov et al. recently examined the elimination of ethane from the dimethylplatinum(IV) complex $Cs_2[Pt(CH_3)_2Cl_4]$.[70–73] When this reaction is carried out in D_2O, multiple deuteration is observed in the ethane produced. The range of ethane isotopomers observed in this reaction ($C_2H_{6-i}D_i$: 1:0.85:2.0:2.2:0.2:0.3:0.3 for $i = 0-6$, respectively) indicates that H/D exchange is largely localized on one of the carbon centers. Furthermore, if $[PtCl_6]^{2-}$ is present in the reaction mixture, ethyl chloride is generated. The results of the H/D exchange resemble that obtained for an isolable ethyl(hydrido)rhodium(III) complex proposed to undergo isotopic exchange through an ethane σ adduct.[74]

The proposed mechanism shown in Scheme 6 accounts for these observations. Formation of intermediate **L** (step (a)) can either result in elimination of ethane (step (b)) or loss of a proton to generate the ethylplatinum(II) complex **M**. This



Scheme 6. Proposed decomposition pathway for $[Pt(CH_3)_2Cl_4]$ in aqueous solution at 95 °C.

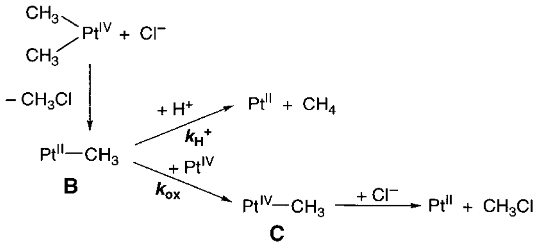
compound can then undergo a reversible protonation reaction which leads to multiple deuteration of the ethyl group in the presence of D^+, or reaction with Pt^{IV} to produce the ethylplatinum(IV) species **N**, which decomposes into ethyl chloride and Pt^{II}. Intermediate **L** may be either a Pt^{II}–ethane σ adduct or an ethyl(hydrido)platinum(IV) species. Zamashchikov et al. have argued for the intermediacy of the latter on the basis of isotope effects;[71] however, their analysis assumes that σ-adduct formation from free Pt^{II} and alkane exhibits no isotope effect. Recent evidence indicates that this is not a valid assumption.[75–77] In a related study, two-electron reduction of $[Pt(CH_3)Cl_5]^{2-}$ in D_2O yields no H/D exchange, whereas multiple deuterium incorporation is observed in CD_3OD.[56] While the data from the such studies cannot directly distinguish between the mechanistic alternatives, the results are completely consistent with the sequence shown in Scheme 5.

A recent theoretical study by Siegbahn and Crabtree examined the mechanism of C–H activation by platinum(II).[59] The data indicate that the energy barrier for a reaction proceeding through $[Pt^{IV}(R)(H)]$ is somewhat lower than for a single-step, non-redox mechanism. Nevertheless, the authors argued in favor of the single-step mechanism for Pt^{II} based on analogy to Pd^{II}, which can effect similar chemistry. The +4 oxidation level is prohibitively high in energy for palladium. In summary, all of the results to date are consistent with the presence of both Pt^{II} σ adduct and $[Pt^{IV}(R)(H)]$ intermediates; formation of RPt^{II} (**B**, Scheme 1) arises from deprotonation of $[Pt^{IV}(R)(H)]$ (Scheme 5).

2.1.5. Other Mechanistic Studies: The Fate of RPt^{II} under Catalytic Conditions

As suggested in Scheme 1, the alkylplatinum(II) intermediate **B** can undergo protonolysis to regenerate the alkane or two-electron oxidation to produce the alkylplatinum(IV) intermediate **C**. Because step (b) in Scheme 1 appears irreversible under catalytic conditions, the relative ratio of these reaction rates can have important implications on the reaction selectivity. Two groups have examined this competition directly by the in situ generation of **B** in solutions containing varied concentration of H^+ and platinum(IV).[49, 55, 70] Nucleophilic attack by chloride on $[Pt^{IV}(CH_3)_2Cl_4]^{2-}$ at 95 °C in aqueous solutions liberates CH_3Cl and $[Pt^{II}(CH_3)Cl_3]^{2-}$ (see structure **D**, Figure 2). Zamashchikov and co-workers identified a branching ratio of the secondary rate constants k_{ox}/k_{H^+} of about 18 (Scheme 7).[70]

In related experiments, a ratio k_{ox}/k_{H^+} of about 1 was obtained at room temperature when **B** was prepared by reduction of $[Pt^{IV}(CH_3)Cl_5]^{2-}$ with cobaltocene,[55] and a value for k_{ox}/k_{H^+} of 70 was found for an ethylplatinum(II) complex at 80 °C.[49] Although the origin of these differences is not entirely clear, it appears that the ratio is larger at higher temperatures. Under catalytic conditions (typically 120 °C), the oxidation of **B** by Pt^{IV} is likely much faster than the protonolysis reaction. These results explain why no deuterium incorporation was observed in hydrocarbon substrates when the catalytic reaction was carried out in D_2O.[58, 78] This confirmation that C–H activation is the rate-determining step emphasizes the importance of understanding the detailed mechanism of this reaction.



Scheme 7. Determination of the relative rate constants for the protonation and oxidation of **B**.

2.2. Recent Advances in Platinum-Catalyzed Alkane Oxidation

2.2.1. Studies on the Selectivity of C–H Activation

The alkane oxidation system discovered by Shilov is especially attractive because of the unique selectivity patterns observed.[8] The reactivity contrasts with that effected by radical reagents both from the standpoint of regio- and chemoselectivity. With respect to regioselectivity, reactions with linear alkanes often lead to selective chlorination/hydroxylation at the methyl positions rather than at the weaker, secondary C–H bonds. The chemoselectivity of the reaction is reflected by the initial oxidation products being relatively stable to overoxidation. Several recent studies have examined the scope of this reaction selectivity to identify its potentially practical utility.[53, 58, 79–84]

Methane is perhaps the most attractive substrate for direct oxidation to its alcohol product, since it is by far the most abundant alkane and represents an enormous natural resource for use as a fuel and as a chemical feedstock.[1] Results published by Sen et al.[83] and Labinger, Bercaw et al.[80] indicate that methane and methanol exhibit similar reactivity with respect to the platinum salts under standard oxidation conditions. Unfortunately, the similarity in rates combined with the greater solubility of methanol in water will limit the practicality of this system. Nevertheless, this selectivity stands in sharp contrast to that for reactions involving hydrogen-atom abstraction, where methanol can be expected to react up to six orders of magnitude faster than methane.

Further support for the unique selectivity patterns was obtained by oxidation of the C_2 substrates ethane and ethanol.[53, 58, 79, 83] Here the relative rate of C–H bond activation follows the order $H–CH_2CH_3 > H–CH_2CH_2OH >$

H–CH(OH)CH$_3$, which is opposite to that expected on the basis of bond dissociation energies. Recent mechanistic studies by Sen and co-workers indicate that Zeise's salt, $[PtCl_3(C_2H_4)]^-$, is an intermediate in the oxidation of both ethane and ethanol.[83] These results support the viability of direct oxidation of ethane to ethylene glycol! An industrial process based on such technology would be a very attractive alternative to the oxidation of ethylene.

The water-soluble substrate *p*-toluenesulfonic acid is oxidized at the methyl group 1.5 times faster than the corresponding hydroxymethyl group of the product.[58] No oxidation of the aldehyde product was observed. Furthermore, use of *p*-ethylbenzenesulfonic acid reveals comparable rates of functionalization at both the methyl and benzylic positions. Sen and co-workers have also noted the importance of the "chelate effect" in the oxidation of functionalized organic substrates such as aliphatic alcohols, carboxylic acids, sulfonic acids, and phosphonic acids.[81, 82, 84] In their studies, they observe the following order of reactivity: $\alpha\text{-CH} \ll \beta\text{-CH} < \gamma\text{-CH} < \delta\text{-CH}$ for alcohols and $\alpha\text{-CH} \ll \beta\text{-CH} < \gamma\text{-CH} \geq \delta\text{-CH}$ for acid substrates. The trends support a reaction pathway involving initial substrate coordination to the platinum center followed by substrate activation. Thus, in addition to the inherently unusual selectivity patterns observed in Shilov chemistry, the "chelate effect" can also be employed to enhance selectivity and direct the oxidation chemistry to typically unreactive C–H bonds.

2.2.2. Substitution of Pt^{IV} with Less Expensive Oxidants

One of the most formidable challenges facing the use of the Shilov system is replacing Pt^{IV} with an economically viable oxidant. Although numerous high-potential oxidants will convert the alkylplatinum(II) intermediate **B** into the alkylplatinum(IV) species **C**, the challenge lies in identifying a reagent which will not irreversibly oxidize the Pt^{II} catalyst as well. Platinum(IV) does not encounter this dilemma since the reduced product of catalyst oxidation is the catalyst itself [Eq. (11)].

$$Pt^{II} + {}^{*}Pt^{IV} \rightleftharpoons Pt^{IV} + {}^{*}Pt^{II} \qquad (11)$$

Despite several attempts to address this issue, success has been quite limited.[78, 80, 85–87] Shortly after their initial discovery of platinum-mediated alkane oxidation, Gol'dshleger et al. reported that addition of quinones or Cu^{II} to a reaction mixture of $H_2[PtCl_6]/[PtCl_4]^{2-}$ under air led to oxidation of acetic acid to chloroacetic acid which was catalytic in both Pt^{IV} and Pt^{II}.[85] However, only five turnovers were achieved.

Heteropolyacids (also known as polyoxometalates) have also been employed to alleviate the need for stoichiometric amounts of Pt^{IV}.[86, 87] $Na_8HPMo_6V_6O_{40}$ (HPA-6) was added to the standard reaction mixture in order to couple alkane oxidation to O_2; the reduced form of HPA-6 can be reoxidized by O_2. Although up to two turnovers were observed, the methanol generated in the reaction was typically overoxidized.[86] Another heteropolyacid, $H_3PMo_{12}O_{40}$ (phosphomolybdic acid), was successfully employed as a redox mediator for the electrocatalytic oxidation of *p*-toluenesulfonic acid under bulk-electrolysis conditions (+0.7 V vs. Ag/AgCl at 120 °C).[87] In this case, no Pt^{IV} was added to the initial reaction mixture. Nevertheless, after about six turnovers (with respect to Pt^{II}) overoxidation of the alcohol product was observed, likely due to deposition of Pt^0 which was observed at longer reaction times.

Recently, Horvath and co-workers reported the oxidation of methane by Cl_2 mediated by platinum salts in aqueous solution.[78] While no deposition of metallic platinum is observed in this reaction, overoxidation products are still obtained after several hours at 125 °C. Thus, despite several attempts to circumvent the requirement for Pt^{IV} with a variety of stoichiometric oxidants and/or redox mediators, success remains elusive. (A recent exception is discussed in Section 3.2).

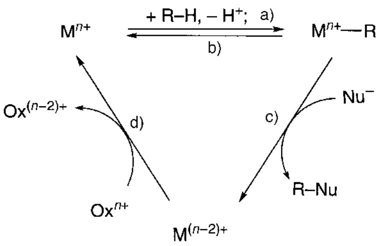
2.3. Future Challenges

The platinum-mediated chemistry described above has been fruitful for exploring a range of mechanistic and selectivity issues related to alkane oxidation by homogeneous transition metal complexes. Unfortunately, several features render it impractical in large-scale reactions. The previous section outlined some of the difficulties involved in replacing Pt^{IV} as the stoichiometric oxidant. Practical applications will clearly require the use of a less expensive reagent, preferably O_2. The selectivity of these reactions also does not appear sufficiently high for large-scale implementation. Deposition of platinum metal further erodes the characteristic selectivities of the homogeneous reaction, and unlike palladium(0), which is often reoxidized in catalytic reactions, reduction to platinum(0) appears much less reversible. These issues must be addressed in order to develop a useful system for platinum-mediated alkane oxidation. The next section will demonstrate that many of these problems can been circumvented by using different transition and main group metals and alternative solvents.

3. Alkane Oxidation by Electrophilic Metal Ions in Strong Acid Media

3.1. Overview

Considerable attention has recently been directed toward the oxidation of alkanes by electrophilic metal ions in strong acid media. At first glance, these systems seem quite similar to the platinum complexes used in aqueous media discussed above. For example, the overall reaction appears consistent with an electrophilic C–H activation followed by subsequent oxidation/functionalization. However, many of the metals are in their highest stable oxidation state (e.g., Hg^{2+}, Co^{3+}), suggesting that an alternative mechanism may be operating. One possibility, shown in Scheme 8, has the functionalization step preceding the oxidation step, thereby avoiding the unstable $M^{(n+2)+}$ oxidation level. This mechanism suggests the organometallic intermediate RM^{n+} is susceptible to both electrophilic (step (b)) and nucleophilic attack (step (c)).



Scheme 8. Proposed catalytic cycle for the oxidation of alkanes by various metal ions (e.g., Hg^{II} and Pd^{II}) in strong acid solvents.

Other mechanisms (e.g., outer-sphere electron transfer) have also been proposed, and these studies remain the subject of current research efforts. Importantly, several of these systems demonstrate the viability of using O_2 as the terminal oxidant for alkane oxidation.

3.2. Metal-Catalyzed Oxidation of Methane by Sulfuric Acid

The mercury(II)-mediated system discovered by Periana and co-workers at Catalytica represents a major advance for the direct, selective oxidation of methane.[22, 23] This reaction, shown in Equation (12), can be carried out in a variety of

$$CH_4 + 2\,HgX_2 \xrightarrow{HX} CH_3X + HX + Hg_2X_2 \qquad (12)$$
$$X = CF_3SO_3,\ HSO_4,\ CF_3CO_2$$

strong acid solvents; it is unsuccessful in weaker acids such as acetic acid. Most importantly, in 100% sulfuric acid the reaction becomes catalytic in Hg^{II} [Eq. (13)], generating

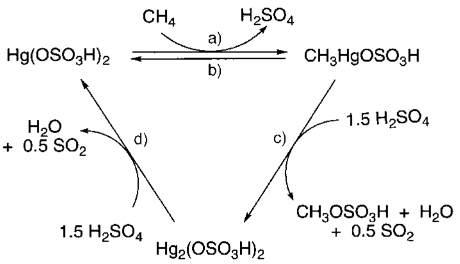
$$CH_4 + 2\,H_2SO_4 \xrightarrow[180\,^{\circ}C]{Hg^{II}} CH_3OSO_3H + 2\,H_2O + SO_2 \qquad (13)$$

methyl bisulfate (CH_3OSO_3H) in 43% yield (85% selectivity at 50% conversion). The high selectivity suggests that CH_4 is about 100-fold more reactive than CH_3OSO_3H. Similar reactivity was observed in trifluoromethanesulfonic and sulfuric acids in the presence of thallium(III), gold(I), palladium(II), and platinum(II)/(IV); however, no efficient catalysis was observed. A potentially viable approach for the direct conversion of methane into methanol using O_2 as the stoichiometric oxidant is shown in Figure 3

$$\begin{array}{lll}
1: & CH_4 + 2\,H_2SO_4 & \longrightarrow CH_3OSO_3H + 2\,H_2O + SO_2 \\
2: & CH_3OSO_3H + H_2O & \longrightarrow CH_3OH + H_2SO_4 \\
3: & SO_2 + 1/2\,O_2 + H_2O & \longrightarrow H_2SO_4 \\
\hline
 & CH_4 + 1/2\,O_2 & \longrightarrow CH_3OH
\end{array}$$

Figure 3. Possible reaction sequence allowing the direct oxidation of methane to methanol by O_2.

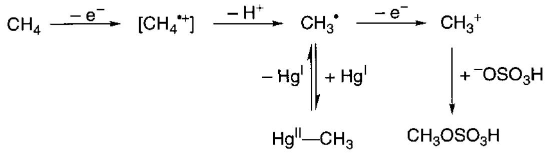
Based on a series of observations, the Catalytica group proposed the catalytic cycle shown in Scheme 9: 1) electrophilic activation of methane to generate a methylmercury(II) intermediate (step (a)), 2) reductive elimination of methyl bisulfate (step (c)), and 3) subsequent oxidation of mercurous bisulfate to regenerate the catalyst (step (d)). As discussed above, the functionalization and oxidation steps have reversed their order relative to the Shilov system (Scheme 1) due to the inaccessibility of mercury(IV).



Scheme 9. Catalytic cycle for the mercury(II)-catalyzed oxidation of methane in sulfuric acid.

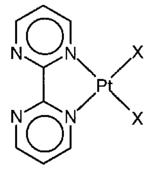
In support of this mechanism, low steady-state concentrations of the methylmercury(II) intermediate are observed under the reaction conditions. When this species is independently prepared, it undergoes competitive reductive elimination of methyl bisulfate (step (c)) and protonolysis (step (b)) in H_2SO_4 at 180 °C with approximately equal rates.[23] When the catalytic reaction is carried out in D_2SO_4, deuterium incorporation into the methane is observed, reflecting the reversibility of the C–H activation step.

The precise mechanism of C–H activation by Hg^{II} remains the subject of some debate. While many of the features of this reaction are consistent with a simple electrophilic substitution mechanism (i.e., deprotonation of a transient Hg^{II} methane σ adduct), Sen and co-workers have recently suggested that an outer-sphere electron transfer pathway may also account for many of the observations.[83, 88] For example, comparison of the reaction between methane and a series of one- and two-electron oxidants (including Hg^{II}) in sulfuric acid led the authors to propose that Hg^{II} was acting as a one-electron outer-sphere oxidant.[83, 88] Formation of methylmercury(II) in the catalytic oxidation reaction can arise by combination of methyl radicals with mercury(I) in solution (Scheme 10).



Scheme 10. Possible electron transfer pathway for the activation of methane by mercury(II) in sulfuric acid.

The stability of CH_3OSO_3H under the reaction conditions is consistent with both mechanistic proposals: The electron-withdrawing OSO_3H group will not only deactivate CH_3OSO_3H toward electrophilic attack but also toward hydrogen-atom abstraction. Moreover, increasing the solvent acidity is expected to increase the reaction rate for both electrophilic and electron transfer pathways. Strong acids enhance the electrophilicity of the metal center because their conjugate bases are weaker ligands. A similar explanation accounts for the higher redox potential of metal ions in strong acids: Less strongly donating ligands are available to stabilize the higher oxidation state. Furthermore, the redox properties of alkanes are dramatically affected by strong acid solvents.[2, 89, 90] Thus, while the outer-sphere oxidation of alkanes by Hg^{II} does not initially appear plausible, the reaction conditions may, in fact, promote such a pathway.



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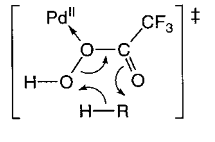
In a more recent development,[91] the reaction in Equation (13) is catalyzed even more efficiently by a bipyrimidine complex of Pt^{II} (**8**): At 200 °C in fuming sulfuric acid, methyl bisulfate can be obtained in over 70 % yield based on methane (90 % conversion, 81 % selectivity). Remarkably, the organic ligand is stable to hot sulfuric acid, probably because the noncoordinated nitrogen atoms are protonated, thus reducing the susceptibility to oxidative degradation. Deposition of platinum metal is not a problem, because the Pt^{II} complex is thermodynamically stable under these conditions; indeed Pt metal can be redissolved by heating under these conditions in the presence of bipyrimidine. The mechanism appears to be closely related to Scheme 1, with step (b)—oxidation of RPt^{II} to RPt^{IV}—being rate-limiting.

3.3. Oxidation of Alkanes with Alternative Late Transition Metals or Solvents

The systems of the researchers at Catalytica were preceded by closely related chemistry involving other late transition metals. Metal ion catalyzed oxidation of hydrocarbons in strong acids has been known for more than two decades,[92, 93] with much of the early work summarized in previous reviews.[26, 94] In 1987, Sen and co-workers extended this chemistry to methane when they reported its palladium(II) acetate mediated oxidation to $CF_3CO_2CH_3$ in trifluoroacetic acid [Eq. (14)].[15–17] Subsequently, a catalytic version of this

$$CH_4 + Pd(O_2CCF_3)_2 \xrightarrow[80\,^\circ C]{CF_3CO_2H} CF_3CO_2CH_3 + Pd^0 + CF_3COOH \qquad (14)$$

reaction was accomplished in trifluoroacetic anhydride with H_2O_2 as the stoichiometric oxidant.[18] The authors suggested that the mechanism may involve electrophilic cleavage of the C–H bond by palladium (step (b) in Scheme 8), or alternatively Pd^{II} activation of peroxyacid generated in situ, leading to methane oxidation through a cyclic transition state (**9**). Unfortunately, several attempts to expand the scope of this chemistry have been complicated by difficulties in reproducing these results.[20, 22, 25, 95]



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The selective oxidation of methane and other lower alkanes by O_2 was observed by Sen and co-workers, who employed 5 % Pd/C and soluble copper(II) salts in a mixture of trifluoroacetic acid and water.[96, 97] Methanol is the primary product of methane oxidation. Carbon monoxide must also be present in the reaction mixture in order to maintain selectivity in the reaction. The necessity of a coreductant bears striking resemblance to reactions of monooxygenase enzymes (e.g., cytochrome P450), which require a reducing agent such as NADH to activate O_2 and effect substrate oxidation. The authors suggest that carbon monoxide reduces O_2 to H_2O_2, which then oxidizes alkanes in the presence of the transition metals. Future mechanistic insights should permit a more detailed comparison with the corresponding biological reactions.

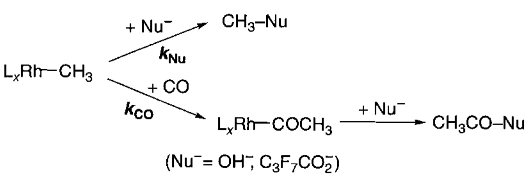
In another system cobalt(III) ions in trifluoroacetic acid were utilized to oxidize methane to $CF_3CO_2CH_3$ (90 % yield based on Co, at 180 °C).[20] Importantly, the methyl ester product is stable to further oxidation under the reaction conditions. Addition of O_2 to the reaction results in a 400 % yield of $CF_3CO_2CH_3$ based on the cobalt(III) oxidizing equivalents available, presumably reflecting reoxidation of Co^{II} by O_2. Examination of the oxidation of ethane and propane by Co^{III} reveals that products of C–C bond cleavage form in addition to the expected alkyl trifluoroacetates.[21] The authors proposed a mechanism involving outer-sphere electron transfer to produce an alkyl radical cation in the first step. This intermediate subsequently undergoes competitive C–H or C–C bond cleavage leading to the observed products. Similarly, rhodium(III) salts also catalyze the oxidation of higher alkanes in trifluoroacetic acid to the corresponding alkyl trifluoroacetates with H_2O_2 as the stoichiometric oxidant.[98]

3.4. Direct Carboxylation of Alkanes Mediated by Late Transition Metals

In a series of recent papers, Sen[24, 99] and Fujiwara[33] have demonstrated the direct carboxylation of alkanes (including methane) catalyzed by rhodium and palladium complexes [Eq. (15)]. These systems not only effect the catalytic functionalization of C–H bonds, but also utilize O_2 as the stoichiometric oxidant.

$$RH + CO + 1/2\,O_2 \xrightarrow{M^{n+}} RCOOH \qquad (15)$$

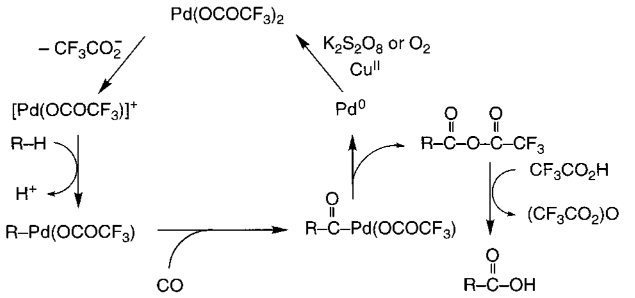
The rhodium-catalyzed reaction, which is carried out in a mixture of perfluorobutyric acid and water, generates both methanol and acetic acid from CH_4, CO, and O_2 at 80 °C.[24, 99] Addition of several equivalents of Cl^- and I^- to the reaction mixture dramatically improves the reaction yields; however, the reason for this effect is currently not fully understood. While the detailed mechanism of this reaction has not yet been determined, the origin of both methanol and acetic acid can be explained by nucleophilic attack (k_{Nu}) competing with CO insertion (k_{CO}) into a rhodium–methyl bond, possibly generated by electrophilic C–H activation of methane (Scheme 11). The ratio of methanol to acetic acid can be



Scheme 11. Possible origin of both methanol and acetic acid in the rhodium-catalyzed carboxylation of methane.

altered by changing the solvent composition. Studies of higher alkanes revealed that C–C bond cleavage is competitive with (and in many cases more favorable than) C–H cleavage. This reaction is effectively a "one-pot" catalytic system capable of both cracking and selectively oxidizing simple alkanes. The authors argue against a radical-cation mechanism that might account for cleavage of the weaker C–C bonds.

The catalytic carboxylation of alkanes such as methane, ethane, propane, and cyclohexane has also been observed with palladium and/or copper salts in trifluoroacetic acid.[27–33] A possible catalytic cycle is shown in Scheme 12. $K_2S_2O_8$ is the oxidant in most of these reactions [Eq. (16)]. A recent report[32] suggests that O_2 can also be used. Mixtures of palladium(II) and copper(II) salts are more effective than either of the metals alone, except for the oxidation of methane where Cu^{II} alone is most efficient. Again, the detailed mechanism of these reactions is not entirely known. Kinetic deuterium isotope effects (3.0–3.2) in the reaction of cyclohexane with Pd^{II}/Cu^{II} or Pd^{II} alone suggest that C–H bond cleavage is involved in the rate-determining step.[29] In contrast, the reactions with Cu^{II} alone do not exhibit a kinetic deuterium isotope effect, which led the authors to propose a radical mechanism.[29]



Scheme 12. Proposed catalytic cycle for the palladium-catalyzed carboxylation of alkanes.

$$\begin{gathered}RH + CO + K_2S_2O_8 + 2\,CF_3CO_2H \xrightarrow{M^{n+}} \\ RCOOH + 2\,KHSO_4 + (CF_3CO)_2O\end{gathered} \tag{16}$$

Unfortunately, the complexity of the above systems has hindered elucidation of the detailed mechanisms. While direct electrophilic alkane activation is an attractive proposal, other possibilities such as radical and/or electron transfer pathways are difficult to rule out.

4. Summary and Outlook

The above reactions involving electrophilic late transition metals offer a promising and potentially practical approach to alkane oxidation. Importantly, the selectivities commonly associated with organometallic C–H activations (e.g., 1° > 2° > 3°) appear attainable in catalytic oxidation reactions as well. The recent examples from Catalytica[22, 91] are especially encouraging since catalytic alkane oxidation in yields of 40–70% are unprecedented!

Meanwhile, a rather clear mechanistic picture has emerged for the catalytic steps of the Shilov system, although open questions remain for the mechanism of C–H activation in Shilov and other systems. Because this step often dictates both the rate and selectivity of the overall reactions, further mechanistic studies appear crucial to the advancement of this chemistry. While oxidative addition of the C–H bond may be possible in the Pt^{II}-mediated reaction, this is not a viable pathway for many of the other systems (e.g., with Hg^{II} or Co^{III}). It is possible, perhaps likely, that a single universal mechanism does not operate for all of the systems.

The solvent appears to play a crucial role in these catalytic systems. In all the examples discussed, the solvent is highly polar and in many cases a strong acid such as sulfuric or trifluoroacetic acid. Do such solvents merely provide a polar, weakly coordinating medium to enhance an electrophilic C–H activation pathway (e.g., involving deprotonation of an alkane σ adduct), or are such solvents necessary to alter the metal and alkane redox potentials to facilitate an electron transfer pathway?

Strong acid solvents also appear to play another role in these reactions, namely esterification of the alcohols produced in the reaction. By doing so, the acids deactivate the products toward further oxidation. For instance, the strong electron-withdrawing groups in $CH_3O_2CCF_3$ and CH_3OSO_3H render them much less reactive toward both electrophilic and radical reagents. Thus, even in cases where one-electron redox/radical chemistry is operating, the selectivity of the reaction can still be quite high, especially in reactions with methane.[88] Clearly, the role of solvent cannot be ignored in these reactions.

The recent advances in this field hold great promise for the future discovery of new, practical approaches to selective, high-yield alkane functionalizations. Such developments will undoubtedly incorporate many of the features described above: product deactivation to prevent overoxidation, oxidatively robust catalysts, and use of inexpensive terminal oxidants (especially O_2). In addition, application of biphasic solvent systems may prove advantageous.[100] For example, a system in which the substrate is more soluble than the product in the catalyst-containing phase should enhance reaction selectivity. Such ideas have been incompletely explored. Furthermore, the interactions between inexpensive terminal oxidants and late transition metal complexes are poorly understood; in many cases such interactions are mediated by other species (e.g., Cu salts or H_2SO_4). Gaining a better mechanistic understanding of this chemistry and exploiting such insight constitute important research challenges for the coming years.

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EVENTS

Arfvedson-Schlenk-Prize

The Gesellschaft Deutscher Chemiker / GDCh (The German Chemical Society) announces that the Arfvedson-Schlenk-Award donated to the GDCh by Chemetall GmbH will be awarded for the first time in autumn 1999. The award is named after the discoverer of the element lithium, Gustav Arfvedson, and the pioneer of lithium organic chemistry, Wilhelm Schlenk.

The Arfvedson-Schlenk-Award intends to honour outstanding scientific and scientific technical achievements in the field of lithium chemistry.

Nominations for the award are to be addressed until the end of the year 1998 to the Geschäftsstelle of the GDCh, Postbox 90 04 40, D-60444 Frankfurt/Main, Germany. Proposals should include the CV of the nominee together with his/her list of publications. Self-nominations are excluded.

The prize-winner will receive the award on the occasion of a ceremonial GDCh session on September 28, 1999 in Goslar on the eve of Chemetall's VI. Hydrid Symposium.

Prof. Dr. J. Heitbaum
Chairman of the Commission