Catalytic Activation of Methane and Ethane by Metal Compounds

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Methane and ethane are the most abundant and the least reactive members of the hydrocarbon family, and their selective conversion to useful chemical products is of great scientific, as well as practical, interest. This review highlights some of the recent advances in the area of low temperature, catalytic, activation and functionalization of methane and ethane. Particular emphasis has been placed on C–H and C–C activation processes leading to the formation of oxygenates.

1
Introduction

Methane is the most abundant and the least reactive member of the hydrocarbon family. Ethane comes second in both categories. Together, they constitute >95% of natural gas, with known reserves approaching that of petroleum [1]. A significant portion of the methane and ethane produced is not utilized because of the difficulty associated with the transportation of a flammable, low-boiling gas. Their possible use as automobile fuels is also limited by the intrinsic disadvantages of gaseous fuels, i.e., low energy content per unit volume and the hazards associated with handling and distribution. Thus, the selective conversion of methane and ethane to more useful chemical products is of great practical interest [2]. For example, three of the highest volume functionalized organics pro-

duced commercially are methanol, formaldehyde, and acetic acid, whose 1995 United States productions were 11.3×10^9, 8.1×10^9, and 4.7×10^9 lbs, respectively [3]. The current technology for the conversion of alkanes to these products involves *multistep* processes: (a) the high temperature steam reforming of alkanes to a mixture of H_2 and CO [4], (b) the high temperature conversion of the mixture of H_2 and CO to methanol [4] and, either (c) the high temperature oxidation of methanol to formaldehyde [5] or (d) the carbonylation of methanol to acetic acid [6], mainly through the "Monsanto process" [7]. Clearly, the *direct*, low temperature conversion of the lower alkanes to the above oxygenates would be far more attractive from an economical standpoint. Of particular interest would be the formation of the *same* end product(s) from different starting alkanes, thus obviating the need to separate the alkanes. For example, natural gas is principally methane with 5–10% ethane. A system that converts both methane and ethane to the same C_1 product would not require the prior separation of the alkanes. Of course, the formation of C_1 products from ethane would require the catalytic cleavage and oxidation of C–C bonds.
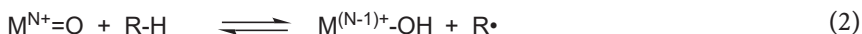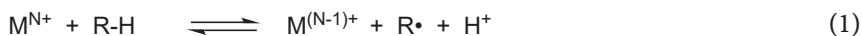
The lack of reactivity of methane and ethane stems from their unusually high bond energies (C–H bond energy of methane: 104 kcal/mol) and most reactions involving the homolysis of a C–H bond occur at fairly high temperatures or under photolytic conditions. Moreover, the selectivity in these reactions is usually low because of the subsequent reactions of the intermediate products, which tend to be more reactive than the alkane itself. Using methane as an example, its C–H bond energy is 10 kcal/mol higher than that in methanol. Therefore, unless methanol can be protected or removed as soon as it is formed, any oxidation procedure that involves hydrogen-atom   ion from the substrate C–H bond would normally cause rapid overoxidation of methanol. The radical initiated chlorination of methane invariably leads to multiple chlorinations [8] (chlorination, however, is more specific in the presence of superacids [9]). In order to achieve the selective functionalization of methane and ethane, it is therefore necessary in most cases to promote a pathway that does not involve C–H bond homolysis as one of the steps. The problem is compounded by the fact that practical oxidation processes require the direct use of dioxygen as the oxidant. Because of its triplet electronic configuration, the reaction between dioxygen and alkanes most often involves unselective radical pathways [10].

In principle, the above selectivity problems can be avoided in suitably designed metal-catalyzed oxidation procedures. Transition metals, particularly those whose most stable oxidation states differ by $2e^-$, often promote nonradical pathways even in the presence of dioxygen [11]. As a bonus, metal ion catalyzed reactions usually operate at low temperatures (<200°C). The use of milder reaction conditions also avoids the loss of selectivity due to overoxidation.

While it is difficult to design a catalytic procedure for the selective functionalization of C–H bonds, it is harder still to achieve catalytic functionalization of C–C bonds even though the C–C bonds are significantly weaker than C–H bonds. Two reasons are usually cited for the general lack of C–C activation compared to corresponding C–H activation by metals [12]. First, C–C bonds are ster-

ically less accessible to transition metal centers surrounded by ligands. Second, metal-carbon bonds tend to be weaker than metal-hydrogen bonds, again due to steric repulsions between the ligands surrounding the metal and the alkyl group bound to it. C–C cleavage is, however, commonly observed in the interaction of bare metal cations with alkanes [13]. In this case, there is no steric hindrance and the metal-carbon and metal-hydrogen bond strengths are comparable (approx. 60 kcal/mol) [13a,b, 14].
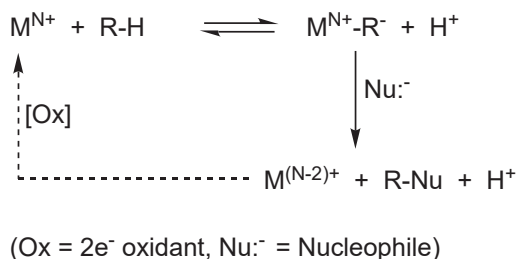
There are three basic metal-mediated alkane activation pathways [15]. The first involves the metal as an 1e⁻ oxidant (Eqs. 1, 2). From a thermodynamic standpoint, the 1e⁻ oxidation of alkanes is generally less favorable than the corresponding 2e⁻ oxidations and, therefore, require the use of either very strong oxidants or relatively high temperatures. Sometimes an auxiliary ligand on the metal may participate in the C–H bond breaking step (Eq. 2). This appears to represent nature's preferred route to alkane C–H activation. For example, it is generally accepted that in the enzyme cytochrome P-450, the species responsible for alkane C–H cleavage is a porphyrinato-Fe(V)=O complex [16]. The C–H activating species in methane monoxygenase has been less well characterized but a high-valent Fe=O species similar to that in cytochrome P-450 has been postulated [17]. The high specificity observed in enzymatic systems is presumably a result of steric restraints. More commonly, however, the organic free radicals generated will participate in a multitude of reaction pathways leading to a large number of products [10].

$$M^{N+} + R\text{-}H \quad \rightleftharpoons \quad M^{(N-1)+} + R\bullet + H^+ \qquad (1)$$

$$M^{N+}{=}O + R\text{-}H \quad \rightleftharpoons \quad M^{(N-1)+}\text{-}OH + R\bullet \qquad (2)$$
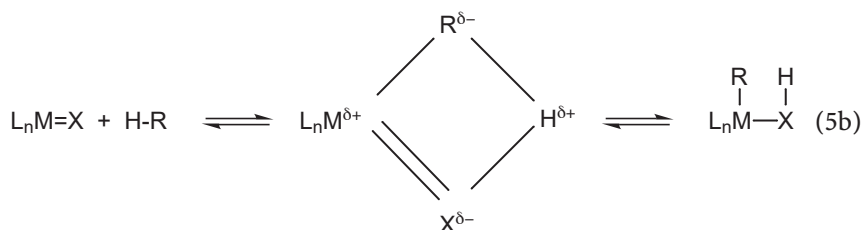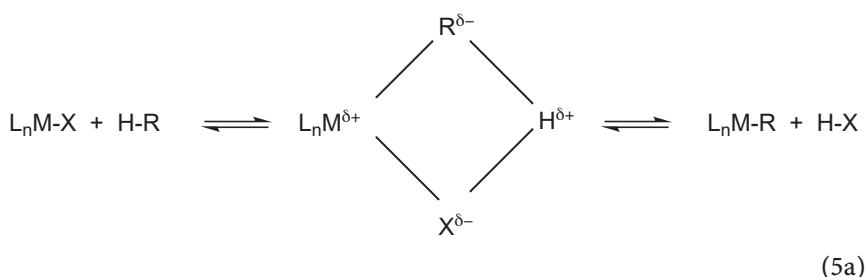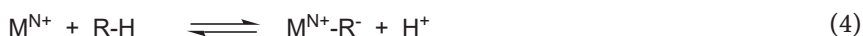
The second C–H cleavage pathway involves the oxidative addition of the C–H bond to a low-valent metal center (Eq. 3) [15]. A two-center version of the oxidative addition reaction described above has also been observed with the porphyrin Rh–Rh bonded dimer complexes [18]. In general, the presence of reactive low-valent metal species prevents the simultaneous presence of most oxidizing agents that are capable of functionalizing the bound hydrocarbyl group in the oxidative addition product. Thus, it is difficult to construct a "one pot" catalytic oxidation procedure, although other types of catalytic functionalizations, including dehydrogenation, are known for higher alkanes [15].

$$M^{N+} + R\text{-}H \quad \rightleftharpoons \quad M^{(N+2)+}{<}^{R}_{H} \qquad (3)$$
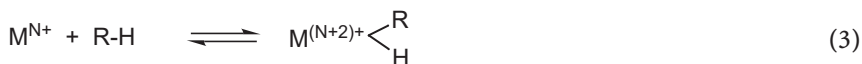
The activation of C–H bonds by an electrophilic pathway is shown schematically (Eq. 4) and has been observed with a number of late transition metal ions [15]. The related four-center electrophilic activation by transition, lanthanide, and actinide metal centers has also been reported (Eq. 5) [15]. A driving force for the former reaction (Eq. 4) is the stabilization of the leaving group, H⁺, by solvation in polar solvents. The most significant advantage of this C–H activa-

$$M^{N+} + R\text{-}H \rightleftharpoons M^{N+}\text{-}R^- + H^+$$

$$M^{(N-2)+} + R\text{-}Nu + H^+$$

(Ox = 2e$^-$ oxidant, Nu:$^-$ = Nucleophile)

Scheme 1.

tion pathway is that the electrophilic metal center can be compatible with oxidants. Therefore, in principle, it should be possible to design a catalytic oxidation procedure that is based on an initial electrophilic C–H cleavage step, as is shown in Scheme 1.

$$M^{N+} + R\text{-}H \rightleftharpoons M^{N+}\text{-}R^- + H^+ \tag{4}$$

$$L_nM\text{-}X + H\text{-}R \rightleftharpoons L_nM^{\delta+} \overset{R^{\delta-}}{\underset{X^{\delta-}}{\diamondsuit}} H^{\delta+} \rightleftharpoons L_nM\text{-}R + H\text{-}X \tag{5a}$$

$$L_nM\text{=}X + H\text{-}R \rightleftharpoons L_nM^{\delta+} \overset{R^{\delta-}}{\underset{X^{\delta-}}{\diamondsuit}} H^{\delta+} \rightleftharpoons L_nM\overset{R\ \ H}{\underset{}{-}}X \tag{5b}$$

Below, we describe catalytic systems for the activation and functionalization of methane and ethane. Rather than a comprehensive review, the account highlights some of the recent advances in the area.

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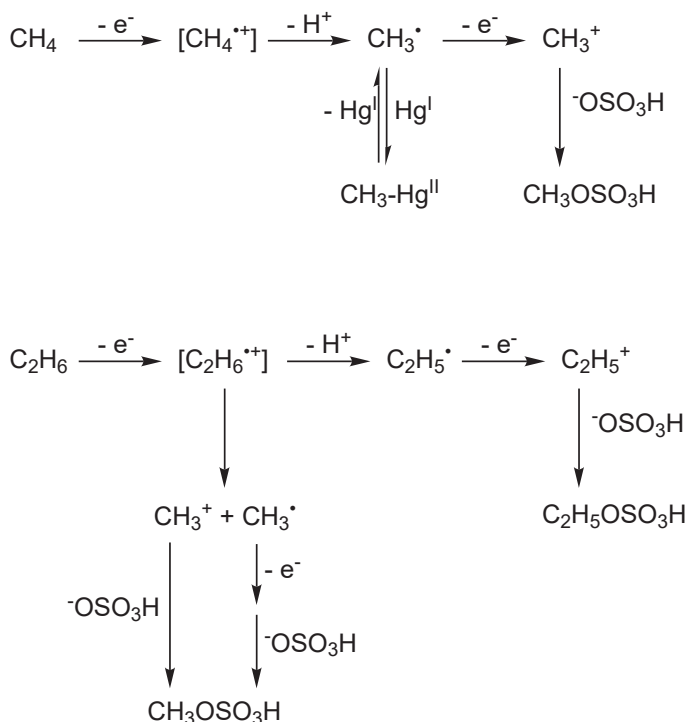## Reactions in Strongly Acidic Media

There has been a number of recent reports on metal-catalyzed electrophilic activation of methane and ethane. For two reasons much of the work in the area has been carried out in strong acids. First, the conjugate bases of strong acids are

poorly coordinating, thereby enhancing the electrophilicity of the metal ion. Second, the esterification of the alcohol, the primary product of alkane oxidation, protects it from overoxidation. One impressive achievement in this area is the Hg(II) catalyzed oxidation of methane to methyl bisulfate (CH_3OSO_3H) in 100% sulfuric acid at 180°C, as described by Catalytica [19]. Both high selectivity and high conversion were achieved. The sulfuric acid served both as the solvent and the reoxidant for the metal. Although an electrophilic mechanism similar to Scheme 1 has been claimed, further studies indicate that a radical pathway, occurring at least in parallel, cannot be ruled out. For example, Sen has observed that a number of free-radical initiators, including $S_2O_8{}^{2-}$, also gave comparable stoichiometric yields of CH_3OSO_3H under conditions where mercury was not reoxidized by sulfuric acid [20]. The $S_2O_8{}^{2-}$ ion is an interesting case in point. Sen has earlier demonstrated that in water at 110°C, $SO_4{}^{-\bullet}$ (generated from $S_2O_8{}^{2-}$)   s a hydrogen atom from methane or ethane to form the corresponding alkyl radical, which is then converted to, inter alia, the alcohol and the bisulfate [21]. In the presence of added carbon monoxide, this radical is trapped efficiently and the resultant acyl radical is ultimately converted to a carboxylic acid. It is therefore possible that, as shown in Scheme 2 [20], one role of *all* the oxidants in sulfuric acid is to generate a methyl radical from methane by outer-sphere electron transfer followed by proton loss. The methyl radical is eventually converted to CH_3OSO_3H. In the special case of Hg(II) as the oxidant, CH_3HgOSO_3H is formed by (reversible) recombination of methyl and Hg(I) radicals. It may be noted that the proposed mechanism is similar to that suggested for some monooxygenases where both the alkyl radical and the alkyl cation, formed by electron transfers to high-valent iron-oxo species, have been implicated as intermediates [22].

The mechanistic scenario outlined above finds support in the reactivity pattern observed with ethane [20]. The radical cation formed from ethane by electron transfer would be expected to fragment some of the time by C–C cleavage (Scheme 2). The direct precedent for such a step is Olah's observation of CH_3NO_2 as the principal product in the reaction of ethane with $NO_2{}^+PF_6{}^-$ [23]. Indeed, the formation of CH_3OSO_3H was observed (up to 25% yield relative to oxidant) when ethane was contacted at 150–180°C in 98% sulfuric acid with any one of a number of radical initiators.

One possible argument against the mechanism shown in Scheme 2 is that the specific metal ions employed are not strong enough oxidants to effect a $1e^-$ oxidation of methane and ethane. However, highly electrophilic metal ions lacking donor ligands have reduction potentials significantly more positive than the corresponding ligated metal complexes. At the same time, there is a dramatic increase in oxidation potential for alkanes in strong acids [24].

The radical-initiated functionalization of methane proceeds even more readily in fuming sulfuric acid (27–33% SO_3 content by weight was employed) [25]. Thus, a variety of radical-initiators were found to convert methane to CH_3SO_3H at 90°C. For every initiator examined, the product concentration was many times the concentration of the initiator (>700 times in the case of $K_2S_2O_8$!). The

$$CH_4 \xrightarrow{-e^-} [CH_4{}^{\bullet+}] \xrightarrow{-H^+} CH_3{}^{\bullet} \xrightarrow{-e^-} CH_3{}^{+}$$

$$-Hg^{II} \Big\updownarrow Hg^{I} \qquad \Big\downarrow {}^{-}OSO_3H$$

$$CH_3\text{-}Hg^{II} \qquad CH_3OSO_3H$$

$$C_2H_6 \xrightarrow{-e^-} [C_2H_6{}^{\bullet+}] \xrightarrow{-H^+} C_2H_5{}^{\bullet} \xrightarrow{-e^-} C_2H_5{}^{+}$$

$$\Big\downarrow \qquad\qquad\qquad\qquad \Big\downarrow {}^{-}OSO_3H$$

$$CH_3{}^{+} + CH_3{}^{\bullet} \qquad\qquad C_2H_5OSO_3H$$

$$\Big\downarrow {-e^-}$$

$${}^{-}OSO_3H \Big\downarrow \qquad \Big\downarrow {}^{-}OSO_3H$$

$$CH_3OSO_3H$$

Scheme 2.

preference for H-atom   ion from methane rather than the methyl group of CH_3SO_3H by the chain carrier, $CH_3SO_3{}^{\bullet}$, may be ascribed at least in part to its electrophilic nature (the "polar effect"). At 170°C, CH_3SO_3H was quantitatively converted to CH_3OSO_3H even in the absence of an initiator. It was also possible to directly convert methane to CH_3OSO_3H by using a radical-initiator and running the reaction at 170°C.

A significant body of work on metal-mediated electrophilic C–H activations has also been carried out in perfluorocarboxylic acids. These build upon Sen's early report on the Pd(II)-catalyzed electrophilic activation and conversion of methane to methyl ester by H_2O_2 in trifluoroacetic acid/anhydride mixture [26]. One noteworthy result in the area is the catalytic carbonylation of alkanes, including methane, in trifluoroacetic acid as reported by Fujiwara [27]. For the most part, the oxidant used was the $S_2O_8{}^{2-}$ ion. Three distinct catalysts, Pd(II), Pd(II)+Cu(II), and Cu(II), were employed. Mechanistic studies, including the examination of the propensity towards ring versus benzylic attack in xylene and toluene, appear to indicate that the first two catalysts activate C–H bonds through an electrophilic pathway whereas alkyl radicals are involved when Cu(II) alone is used as the catalyst. Fujiwara has also employed the copper system for the catalytic aminomethylation of alkanes, including ethane, by *tert*-amine N-oxides [27a].

Moiseev has reported the Co(II)/(III)-catalyzed oxidation of methane and ethane to alcohol derivatives by dioxygen in trifluoroacetic acid [28]. Interestingly, as in the case of oxidation in sulfuric acid, a significant amount of C–C cleavage products were obtained from ethane. A mechanism similar to that shown in Scheme 2 was proposed [28a].

In many of the oxidation reactions carried out in perfluorocarboxylic acids, the corresponding anhydride was added to rapidly esterify the alcohol derived from the alkane. However, as with sulfuric acid, the mechanism of metal-mediated C–H activations in such solvent systems should be approached with caution. For example, Sen has discovered that in the presence of a radical-initiator (e.g., H_2O_2), perfluorocarboxylic anhydrides act as oxidants towards ethane forming the mixed anhydride, $CH_3CH_2COOCOR_f$, and the ketone, $CH_3CH_2COR_f$, in varying ratios [29]. For a fixed amount of initiator, the amount of products formed increased with increasing amount of anhydride employed and was always higher than the initiator added. In particular, with $PbEt_4$ close to 500 equivs. of products were formed from ethane for every equiv. of $PbEt_4$ employed!

The mechanism of this curious reaction involves the formation of $C_2H_5^{\bullet}$ radical, which then attacks $(R_fCO)_2O$ at one of the carbonyl carbons to form an alkoxy radical (Scheme 3) [29]. The attack by the $C_2H_5^{\bullet}$ radical occurs at the most electron deficient site because of the alkyl radical's nucleophilic nature [30]. The alkoxy radical formed undergoes the well-known β-bond cleavage reaction. If the R_f-CO bond is cleaved, the product is the mixed anhydride. On the other hand, if the C(O)-O bond is broken, the ketone is produced. Both pathways produce the $R_f^{\bullet}$ radical: the first directly, and the second by formation and subsequent decarboxylation of the $R_fCO_2^{\bullet}$ radical. The $R_f^{\bullet}$ radical then continues the chain-reaction by   ing a hydrogen from C_2H_6 forming the $C_2H_5^{\bullet}$ radical and R_fH.

Interestingly, unlike ethane, neither methane nor propane is able to participate in this reaction sequence, the former because the C–H bond of methane is too strong to undergo significant hydrogen-atom   ion by the $R_f^{\bullet}$ radical and the latter because only primary alkyl radicals are sufficiently reactive to attack $(R_fCO)_2O$. Thus, Sen's observation of Pd(II)-catalyzed conversion of methane to methanol derivative by H_2O_2 in trifluoroacetic acid/anhydride mixture was not complicated by the above reaction [26, 29].

Finally, there is a recent report on the gas phase oxychlorination of methane using a combination of $PdCl_2$-heteropolyacids as catalysts [31]. The proposed mechanism involves an electrophilic attack on the alkane (Eq. 4). The chlorination of methane catalyzed by platinum supported on superacidic sulfated zirconia has also been reported [32].

Scheme 3.

3
Reactions in Aqueous Medium

Electrophilic C–H activations can also be effected in water. At first glance, water would appear to be particularly unpromising as a solvent for such reactions. Because of their extremely poor coordinating ability (no fully characterized alkane complex is known [33]) alkanes should not be able to compete with water for coordination sites. Moreover, the intermediate metal-alkyl species would be prone to hydrolytic decomposition. In one respect, however, water is almost an ideal medium for C–H functionalization: the O–H bond energy exceeds the corresponding C–H bond energy of even methane. Indeed, the selective oxidation of methane to methanol is carried out by methane monoxygenase in aqueous medium [17].

Shilov and his coworkers were the first to demonstrate metal-mediated alkane functionalization in water [15f]. They showed that simple Pt(II) complexes, such as $PtCl_4^{2-}$, will activate and oxidize the C–H bonds of alkanes, including methane and ethane. Sen [34], Bercaw and Labinger [35], and Horváth [36] have followed up on aspects of Shilov's work and have shown that a wide variety of substrates including methane can be functionalized with unusual selectivity through the mechanism outlined in Scheme 1. Thus, although the homolytic C–H bond energy of methane is 10 kcal/mol higher than that in methanol, a C–H bond of methanol would not be expected to be significantly more susceptible to *electrophilic* cleavage than that of methane. Indeed, Sen has observed that in water at 100°C, the rate constant for the oxidation of methane to methanol by the $PtCl_4^{2-}/PtCl_6^{2-}$ combination (the Pt(IV) species acts merely as a reoxidant for the $Pt^0 \rightarrow Pt^{II}$ step, see Scheme 1) was only one-seventh of that for methanol overoxidation by the same system [34a]. The observed similarity in rates is even more striking given the much higher binding ability of methanol to the Pt(II) center. Moving to substrates with C–H bonds somewhat weaker than that in methane resulted in actual *reversal* of commonly observed selectivity. Thus, the relative rate of C–H bond activation by the Pt(II) ion decreased in the order $H\text{-}CH_2CH_3 > H\text{-}CH_2CH_2OH > H\text{-}CH(OH)CH_3$, i.e., an order that is exactly *opposite* of that expected on the basis homolytic C–H bond energies [34a]. On a practical level, this showed that the direct conversion of ethane to ethane-1,2-diol is possible!

While it has been generally assumed that heterolytic C–H bond cleavage is involved in the Shilov system (Eq. 4), the possibility that C–H activation proceeds through an oxidative addition step (Eq. 3) resulting in the intermediacy of a Pt(IV)(alkyl)(hydride) has been raised based on studies of model systems [37].

The activation and functionalization of C–H bonds by the Pt(II) ion is particularly attractive because of the unusual regioselectivity, high oxidation level specificity, and the mildness of reaction conditions. Nevertheless, thus far it suffers from one crippling drawback: dioxygen cannot be used efficiently as the reoxidant for the Pt^0 formed from Pt(II) during substrate oxidation [38].

4
Miscellaneous Radical Pathways

Two examples of low temperature, catalytic, methane oxidation by hydrogen peroxide should be included in this section. The first involves conversion to methanol using cis-[Ru(2,9-dimethyl-1,10-phenanthroline)(solvent)$_2$](PF$_6$)$_2$ as the catalyst [39]. A ruthenium-oxo species has been proposed as the C–H activating species. In the second report, conversion of methane to methyl hydroperoxide is claimed [40]. The catalyst is a combination of [NBu$_4$]VO$_3$ and pyrazine-2-carboxylic acid. While the mechanism is uncertain, the actual oxidant is believed to be dioxygen with HO• derived from hydrogen peroxide acting as the initiator.

Finally, Crabtree has reported the gas-phase mercury photosensitized reaction of methane with ammonia to yield methylene imine as the ultimate product [41]. Higher imines are also produced if the gas-phase residence time of methylene imine is prolonged.

5
Artificial Monoxygenases

Recently, Sen has reported two catalytic systems which *simultaneously* activate dioxygen and alkane C–H and C–C bonds, resulting in the direct oxidations of alkanes. In the first system, metallic palladium was found to catalyze the oxidation of methane and ethane by dioxygen at 70–110°C in the presence of carbon monoxide [42]. In aqueous medium, formic acid was the observed oxidation product from methane while acetic acid, together with some formic acid, was formed from ethane [42a]. *No* alkane oxidation was observed in the absence of added carbon monoxide. The essential role of carbon monoxide in achieving "difficult" alkane oxidation was shown by a competition experiment between ethane and ethanol, both in the presence and absence of carbon monoxide. In the absence of added carbon monoxide, only ethanol was oxidized. When carbon monoxide was added, almost half of the products were derived from ethane. Thus, the more inert ethane was oxidized *only* in the presence of added carbon monoxide.

Studies indicated that the overall transformation encompasses three catalytic steps in tandem (Scheme 4) [42a]. The first is the water gas shift reaction involving the oxidation of carbon monoxide to carbon dioxide with the simultaneous formation of dihydrogen. It is possible to bypass this step by replacing carbon monoxide with dihydrogen. The second catalytic step involves the combination of dihydrogen with dioxygen to yield hydrogen peroxide [43] (or its equivalent). The final step involves the metal catalyzed oxidation of the substrate by hydrogen peroxide (or its equivalent).

While acetic acid was formed in good yield from ethane, the analogous formation of formic acid from methane proceeded only in low yield because of the general instability of the latter acid under the reaction conditions. Since formic acid is a much less desirable product from methane than is methanol, the possibility of halting the oxidation of methane at the methanol stage was examined.
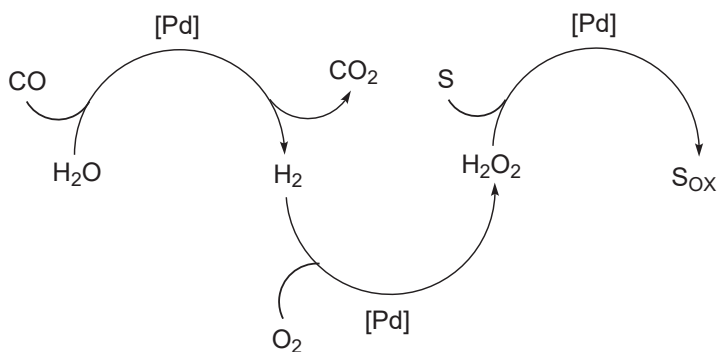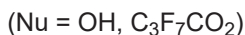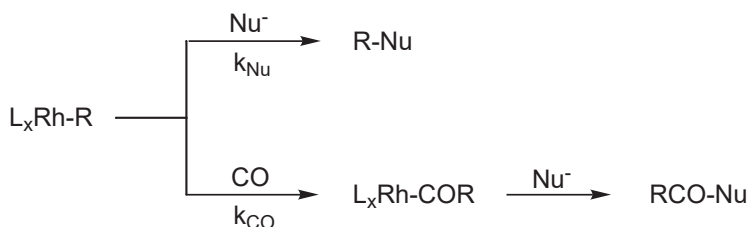
(S = substrate, S_{OX} = oxidized substrate)

Scheme 4.

Simply changing the solvent in the Pd-based catalytic system from water to a mixture of water and a perfluorocarboxylic acid (some water was necessary for the reaction, see Scheme 4) had no significant effect on product composition: formic acid was still the principal product from methane. However, the addition of copper (I) or (II) chloride to the reaction mixture had a dramatic effect. Methanol and its ester now became the preferred products, with virtually no acetic and little formic acid being formed [42b]! The activation parameters for the overall reaction determined under the condition when the rate was first-order in both methane and carbon monoxide were: $A=2\times10^4$ s^{-1}; $E_a=15.3$ kcalmol^{-1}. Since methyl trifluoroacetate is both volatile and easily hydrolyzed back to the acid and methanol, it should be possible to design a system where the acid is recycled and methanol is the end-product.

In the second (slower) system, RhCl$_3$, in the presence of several equivalents of Cl$^-$ and I$^-$ ions, was found to catalyze the direct functionalization of methane in the presence of carbon monoxide and dioxygen at 80–85°C [44]. The reaction proceeded in water to give acetic acid as the principal product [44a]. However, a much higher rate was observed in a 6:1 (v/v) mixture of perfluorobutyric acid and water with the products being methanol and acetic acid [44b]. It is possible to selectively form *either* methanol *or* acetic acid by a simple change in the solvent system. The ratio of alcohol derivative to the corresponding higher acid may be assumed to be a function of the relative rates of nucleophilic attack versus carbon monoxide insertion into a common Rh-alkyl bond (i.e., k_{Nu}/k_{CO}, see Scheme 5). While, to a first-order approximation, k_{CO} is likely to be independent of the solvent, k_{Nu} would depend on the nature of the nucleophile derived from the solvent. Presumably, the perfluorobutyrate ion is a better nucleophile than water since more of the alcohol derivative was formed in perfluorobutyric acid-water mixture than in pure water. This also explains why acetic acid was once again the major product when the perfluorobutyrate ion was tied up as the ester.

$$L_xRh\text{-}R \quad \overset{Nu^-}{\underset{k_{Nu}}{\longrightarrow}} \quad R\text{-}Nu$$

$$L_xRh\text{-}R \quad \overset{CO}{\underset{k_{CO}}{\longrightarrow}} \quad L_xRh\text{-}COR \quad \overset{Nu^-}{\longrightarrow} \quad RCO\text{-}Nu$$

(Nu = OH, $C_3F_7CO_2$)

Scheme 5.

Consistent with the mechanistic scenario shown in Scheme 5 was also the observation that the ratio of acetic acid to methanol derivative formed from methane increased with increasing pressure of CO although the overall reaction was sharply inhibited at high CO pressures.

In addition to Sen's work on the rhodium-catalyzed oxidative carbonylation of methane, Grigoryan has also reported a similar reaction in acetic acid [45]. Predictably, the reaction rate is in-between that observed in pure water and in the perfluorocarboxylic acid-water mixture. Finally, Otsuka has reported the oxidative carbonylation of methane to acetic acid by rhodium-doped iron phosphate [46].

The Pd/Cu and the Rh-based systems show similar selectivity patterns that are, for the most part, without precedent. For example, in both cases, methane is *significantly more reactive* (at least 5 times) than methanol [42b, 44]. However, this does not take into account the increase in the C–H bond energy when methanol is converted to the ester (the following C–H bond-energy data illustrate the point: H-CH$_2$OH, 94 kcal/mol; H-CH$_2$OCOC$_6$H$_5$, 100.2 kcal/mol). For the Rh-based system, even methyl iodide was found to be less reactive than methane [44b]!

A more interesting reactivity pattern exhibited by these two systems is their preference for C–C cleavage over C–H cleavage for higher alkanes [42b, 44b]. Indeed, we are unaware of any other catalytic system that effects the oxidative cleavage of alkane C–C bonds under such mild conditions. For example, the Rh-based system converts ethane to a mixture of methanol, ethanol, and acetic acid, with the ratio of products formed through C–H versus C–C cleavage of approx. 0.6 on a per bond basis [44b]. As with methanol, control experiments indicated ethane is more reactive than ethanol. Additionally, neither ethanol nor acetic acid is the precursor to methanol. Finally, even part of the acetic acid is formed by initial C–C cleavage of ethane followed by carbonylation of the resultant C$_1$ fragment. For C$_4$ and higher alkanes, C–C cleavage products were *virtually all* that were observed; specially noteworthy was the formation of ethanol from n-butane, which indicates that vicinal diols are not the precursors to the C–C