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Alkane C–H activation and functionalization with homogeneous transition metal catalysts: a century of progress—a new millennium in prospect

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The main advances in the title area are reviewed with emphasis on catalytic alkane functionalization, both organometallic and bioinorganic. Current challenges are discussed. A tunable, selective hydrocarbon functionalization is still out of reach and resolving mechanistic problems has proved particularly challenging.

The field of alkane activation and functionalization has taken a strong hold on chemists' imaginations because it poses hard challenges. The central problem is simply to develop ways to replace selected H substituents of alkanes by any of a variety of functional groups, X (eqn. (1)). Progress has been slow—in spite of substantial work on the problem, we are still far from the goal. The field has also raised hard mechanistic questions that have led to controversies that were only settled with the development of new mechanistic probes.

$$C–H \rightarrow C–X \qquad (1)$$

Born in London in 1948, Robert Crabtree was an undergraduate at Oxford with Malcolm Green. He worked with Joseph Chatt for his Ph.D. at Sussex University and then with Hugh Feklin at the CNRS, Gif, France for four hours years, first as a post-doctoral associate, then as Attaché de Recherche. He has been on the Yale faculty since 1977. He has obtained the ACS and RSC organometallic chemistry awards and the Bailar Medal of the University of Illinois. His interests include catalytic CH activation and functionlization, metal hydrides and hydrogen bonding, oxidation and the bioinorganic chemistry of photosynthetic oxygen evolution.

This field is not only of academic interest. Conversion of methane to methanol is of significant practical interest (eqn. (2)) in relation to energy production. Methane from natural gas is available in very large amounts at remote sites, but, as a permanent gas, methane cannot be transported economically. Conversion of the methane into a transportable liquid, such as methanol (eqn. (2)), would make remote gas a viable energy source. Another practically important application would be the conversion of *n*-alkanes to linear alcohols or carboxylic acids.

$$CH_4 + \tfrac{1}{2}O_2 \rightleftharpoons CH_3OH \qquad (2)$$

Selectivity like that of eqn. (2) is hard to achieve chemically. Partial oxidation products such as methanol are desirable, but overoxidation is easy, in this case to give CO_2. The low reactivity of alkanes in general means that either severe conditions or highly reactive reagents must be used. In either case, more than one possible product can often be formed, degrading selectivity.

A number of enzymes also exist that oxidize unactivated CH bonds, usually *via* hydroxylation. Indeed, alkane activation is reminiscent of N_2 fixation[1] to give NH_3 and water oxidation[2] to O_2 in the sense that all three problems involve unreactive substrates, a reaction of potential commercial importance and in each case a metalloenzyme exists that carries out the key reaction. For methane conversion, this is methane monooxygenase[3] (MMO) with its di-iron oxo cluster active site,[1] for N_2, nitrogenase, with an Fe_7MoS_9 active site cluster, and for water oxidation, Photosystem II, with a tetramanganese active site. In each case, model compounds have also been studied in detail.[4]

This 'Perspective' is not intended to replace the standard reviews in the field,[5–8] still less to be exhaustive, but only to treat some key ideas and findings for the general reader.

Thermodynamics and kinetics

Many alkane reactions, such as dehydrogenation to alkenes, are endothermic. No matter how good a catalyst is used, they need to be driven in some way. Typical strategies, also discussed in more detail below, include use of an alkene as sacrificial hydrogen acceptor and of photochemical methods, where the photon energy drives the reaction.

Exothermic reactions often result from inserting an electronegative element into the C–H bond. Chief among these is alkane hydroxylation—for example, eqn. (3) is always exothermic by at least 30 kcal mol^{-1}.

$$\tfrac{1}{2}O_2 + R–H \rightarrow ROH \qquad (3)$$

Many other primary oxidants can also be envisaged. Mayer[9] has discussed a convenient guide to estimating the thermodynamics. Different primary oxidants, XO (eqn. (4)) and different hydrocarbons (eqn. (5)) are compared.[10] Summation of

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Table 1 Thermodynamics ($\Delta H°$) of C–H bond homolysis, C–H hydroxylation and O donation from primary oxidants[a]

R	R–H ⟶ R• + H•	R–H + O ⟶ R–O–H
Me	104.9	−89.8
Et	101.1	−95.6
i-Pr	98.6	−99.6
t-Bu	96.5	−102.0
X–O	**X–O ⟶ X + O**	
O_3	25	
H_2O_2	34	
N_2O	40	
$½O_2$	60	
C_5H_5NO	72	
Me_2SO	87	

[a] In kcal mol^{-1}, gas phase. Adapted from ref. 4 with permission.

the $\Delta H°$ terms for the two parts then gives the $\Delta H°$ of the overall reaction (eqn. (6), Table 1).

$$XO = X + O \quad (4)$$

$$O + RH = ROH \quad (5)$$

$$XO + RH = ROH + X \quad (6)$$

Kinetic factors determine selectivity, a key issue in alkane functionalization. The classical organic approach involves use of a radical, such as HO• or RO•, for which H abstraction from alkane is exothermic. This in turn relies on O–H bonds usually having bond strengths comparable to or greater than those of aliphatic C–H bonds (*e.g.*, HO–H, 119 kcal mol^{-1}). Selectivity between different CH bonds is then also governed by the bond strength trends (tert. CH < sec. CH < prim. CH < CH_3–H; see Table 1) leading to the order of relative reactivity: tert. CH > sec. CH > prim. CH > CH_3–H.

More recently, superacid electrophiles have been shown to abstract H^- ion from an alkane.[7] The selectivity depends on the relative stabilities of the resulting series of carbocations; abstraction from tert. CH is also favored and leads to the same relative ordering as seen for radical reactions.

Provided that they do not rely on H atom or H^- ion transfer, transition metal reagents need not follow the classical selectivity pattern. Those that operate by oxidative addition (eqn. (7),

$$RH + L_nM \rightleftharpoons L_nM(R)(H) \quad (7)$$

where L_nM is a metal and its ligand set) tend to attack at the least hindered terminal methyl group, making them potentially useful for synthesis of the desirable linear functionalized alkanes *versus* the branched species that result from radical or electrophilic reagents.

The selectivity issue has been dramatically highlighted by the 'Barton challenge'.[11] This was devised by John D. Roberts, emeritus professor of chemistry at Caltech, in honor of the late Derek Barton. It consists of a prize of $5000 for a chemical system that converts *n*-hexane to adipic acid with 85% yield based on alkane converted. This obviously requires high selectivity for attack at terminal methyl groups over both internal CH_2 groups and CH_2 groups adjacent to the first carboxyl group introduced, something not achievable by any known chemical route.

For oxidative addition, hundreds of examples of H_2 addition were known (eqn. (8)) before a C–H case was found. It was

$$H_2 + L_nM \rightleftharpoons L_nM(H)_2 \quad (8)$$

puzzling that hydrogen, as the zeroth member of the hydrocarbon series, should be so much more reactive than methane, the first member, particularly since their bond strengths are very similar. The kinetic reactivity of H_2 has now been traced[12] to the omnidirectional character of the H(1s) orbital *versus* the directed nature of the corresponding $CH_3(sp^3)$ bonding orbital in methane; the H atoms of H_2 can therefore both form strong partial bonds to two or more atoms in the relevant transition states, while a CH bond has only one H. This argument also explains why C–C bond cleavage in alkanes is exceptionally rare:[13] two directed orbitals are now involved. There is also often a greater thermodynamic driving force for H_2 reactions *versus* C–H or C–C cases, because X–H bonds tend to be stronger than X–CH_3 bonds.

Arenes are much more reactive than alkanes in CH bond cleavage reactions, in spite of the greater strength of arene *versus* alkane CH bonds. For example, arene auration and mercuration have long been known.[14] Arenes are more reactive kinetically probably because the arene CH bond is less hindered and the metal can interact with the ring prior to CH cleavage,[15] and thermodynamically, because of the stronger aryl *versus* alkyl C–M bonds in the product.

Organometallic *versus* coordination chemistry

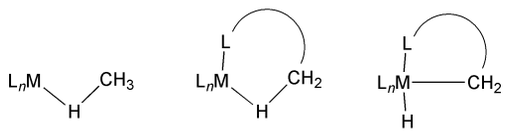
The field naturally divides into subareas, given in order of decreasing interaction between metal and alkane. The organometallic approach involves direct interaction of the metal with the alkane, followed by C–H bond breaking and formation of M–C bonds, usually *via* oxidative addition. This is generally found for organometallic systems, where the reactive metal fragment (L_nM) has ligands such as cyclopentadienyl (Cp), phosphines or CO. Typical metals are 2nd and 3rd row transition elements. One is normally dealing with diamagnetic complexes and two-electron chemistry. By avoiding radical or electrophilic pathways and intermediates, this choice tends to give desirable 'Barton challenge' selectivity (prim. CH > sec. > tert.). Since organometallic species are often destroyed by strong oxidants, this approach is normally only applicable to alkane functionalization reactions where either weak oxidants or no oxidants are used.

In contrast, the coordination chemistry approach[4] is rooted in an attempt either to understand or to mimic selective alkane oxidations carried out by a variety of enzymes; the metals employed are usually the biologically important inorganic elements, Fe, Co, Cu and Mn, or analogues of these, *e.g.*, Ru. Two types of mechanism can occur. The first type involves initial direct interaction of the alkane with a ligand of the complex, such as transfer of an H atom or hydride ion to a metal oxo group. More commonly, the metal complex catalyzes the decomposition of the primary oxidant to generate reactive oxidant-derived fragments, typically O-centered radicals, that attack the alkane. The first 'direct' pathway is thought to be adopted in enzyme reactions, hence the greater interest in this type. The second 'indirect' pathway is usually considered less desirable because of its tendency to give poorer selectivity and because it uses pathways already well-established in organic chemistry. Both 'direct' and 'indirect' pathways tend to have a selectivity that broadly resembles that of radical reactions (tert. CH > sec. > prim.). Distinguishing the direct and indirect situations has proved surprisingly difficult, however.

Organometallic complexes and catalysts

Most work in this area has been directed towards one of three goals: simple alkane complexation without CH bond cleavage, stoichiometric alkane reactions and catalytic alkane conversion. True alkane complexes, represented here as $L_nM(HR)$ (**1**), where the alkane RH is intact, are still very rare. As a result, most reports in this area have been concerned with agostic complexes (**2**), where binding of an alkyl group to the metal is promoted by the chelate effect. Stoichiometric alkane reactions

are also relatively rare but once again, chelation can drive CH addition to the metal in the cyclometalation product (**3**). Catalytic alkane conversion has been the most difficult of the three goals and there are still only a limited number of examples and of reaction types.



1 **2** **3**

Activation *versus* functionalization

Alkane 'activation' refers to binding of an alkane CH bond to a metal, normally with cleavage of the bond by oxidative addition (eqn. (9)).

$$L_nM + R{-}H \rightleftharpoons L_nM(H{-}R) \rightleftharpoons L_nM(R)(H) \quad (9)$$

Alkane functionalization, in contrast, involves replacement of a C–H hydrogen by an organic functional group X. This may be catalyzed by a transition metal complex, in which case it may go through the intermediates shown in eqn. (9), but it is essentially an organic reaction in which the activation has to be followed by a functionalization step. The latter has proved more difficult than the activation step, however, since alkyl hydride complexes tend to release alkane on attempted functionalization.

Alkane and agostic complexes

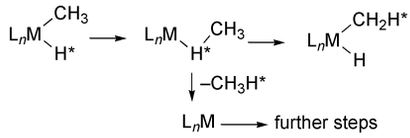
Because they are both very weak σ-bases and π-acids, alkanes are among the least effective species to act as ligands for transition metals. Like other X–H molecules (X = H, R_3Si, R_2B...) alkanes can form σ-complexes[16] with metal fragments that can π-back bond. The requirements for alkanes to bind successfully seem to be the presence of a low valent metal and the absence of competitive decomposition pathways. Enhanced metal to alkane π-back donation into C–H σ* orbitals causing enhanced metal–alkane binding parallels the pattern seen for molecular hydrogen complexes,[17] where stable binding also becomes possible when the metal π-back bonds into the H–H σ* orbital. For both CH_4 and H_2, when back donation becomes very strong, the C–H or H–H bond is cleaved and the oxidative addition product is formed. Indeed, a continuum of situations can be found in different complexes in which the C–H or H–H bond is progressively elongated. For the H_2 case, these are denoted as 'stretched' dihydrogen complexes.[16] This means that alkane binding in this way is more likely for low valent, 2nd and 3rd row organometallic compounds than for 1st row coordination compounds, because the former are usually much stronger π-bases.

A key feature of alkane binding is the acidification of the CH bond. This is also seen, but in more pronounced form, in the much better studied case of dihydrogen complexation, where free H_2 ($pK_a = 35$) is often acidified by a factor of $>10^{20}$ because the pK_as of dihydrogen complexes often lie in the range 0–15. This acidification results from the predominant donation of C–H σ electrons to the metal acceptor orbital, leading to a net positive charge on the ligand, little attenuated by the relatively less important M(d_π) to CH (σ*) back donation.

Authentic alkane complexes were first detected by UV/vis spectroscopy in an alkane matrix at low temperature after photoexpulsion of CO from the hexacarbonyl precursor.[18]

$$M(CO)_6 \xrightarrow{h\nu,\ \text{alkane}} M(CO)_5(\text{alkane}) \quad (10)$$

The intermediacy of alkane complexes was also required to explain the isotope exchange data and inverse kinetic isotope effects in a number of reactions involving reductive elimination of labeled methyl hydrides. These showed isotope scrambling in the starting material isolated after partial reaction (eqn. (11)).[12,19]



(11)

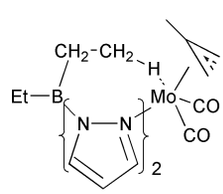
In one case (L_nM = Tp*Rh(CNCH$_2$*t*-Bu)), Jones[20] found that in benzene, the final product, $L_nM(Ph)H$, was formed with a rate dependent on the PhH concentration. This suggests associative substitution of the benzene is required to displace CH_4, so the methane complex must be strongly bound.

Early observations from the Shilov system[5] (discussed in detail below) can perhaps best be interpreted in terms of the formation of alkane complexes as intermediates. Methane was found to undergo multiple H/D exchange with CH_3COOD catalyzed by $[PtCl_4]^{2-}$, even at very early reaction times, implying that the initially monodeuterated methane does not immediately leave the coordination sphere of the Pt(II) but rather remains bound and undergoes further isotope exchange steps.

Only recently have alkane complexes been isolated for complexes in unexceptional situations. $CpRe(CO)_2$(*n*-heptane) was detected by FTIR at room temperature in heptane.[21] $CpRe(CO)_2$(cyclopentane) was detected by NMR and showed fluxional behavior with fast 1,1′- and 1,2-migration of the metal.[22] Another case is an iron porphyrin equipped with a cap that provides a void that encapsulates the alkane, *n*-heptane. In this case a crystal structure was obtained.[23]

Theoretical work suggests that a tightly bound alkane intermediate complex, $[Ir(OOCCF_3)(PH_3)_2(H{-}CH_2CH_2CH_3)]$, can undergo 1,1′-migration to allow the metal to migrate from one H to another within the terminal methyl group much more readily than it can migrate to more distant CH bonds.[24]

In the area of chelate assisted C–H binding, early observations by Cotton on **4** established the existence of such complexes. These species were named 'agostic' complexes and gained greater attention with Brookhart and Green's key 1983 review.[25] The C–H–M bridge tends to be bent with the C–H bond elongated relative to the unbound state. These agostic species can be in equilibrium with the C–H oxidative addition product as in eqn. (12).



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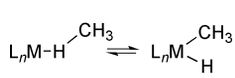


(12)

Plotting the conformational data for a series of agostic compounds allowed us to propose a kinetic pathway for the CH approach to the metal, which, in the extreme of strong metal/CH interaction, results in the complete scission of the C–H bond in an oxidative addition reaction;[26] this later found support from theory.[27]

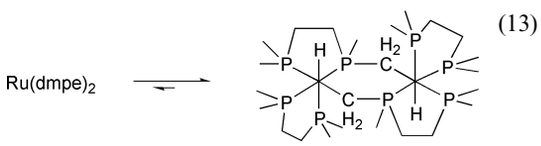
The σ-donation component of the M–(HC) bonding[16] slightly lengthens but does not break the C–H bond; in contrast, when back donation into the C–H σ* orbital becomes dominant, oxidative addition occurs. The ^1J(C,H) coupling

constant in the NMR spectrum and the lowering of the *ν*(CH) stretch in the IR spectrum both correlate with bond stretching. In rare cases, neutron diffraction has given definitive C–H bond distances, but the more common X-ray studies are less accurate.

Where an agostic methyl is present, the metal can readily undergo 1,1′-migration with rotation of the methyl group.[25] In such a case, NMR spectroscopy shows a single resonance for all three methyl hydrogens and the situation can be hard to distinguish from the case where the methyl group is unbound. Fortunately, the isotope perturbation of resonance (IPR) experiment can distinguish[28] a free CH_3 from a bound CH_3 with fast rotation. In this experiment, the partially deuterated methyl gives separate resonances for the CH_3, CH_2D and CHD_2 isotopomers as a result of the preference for H rather than D to be in the bridging site, leading to a difference in the way the averaging takes place.

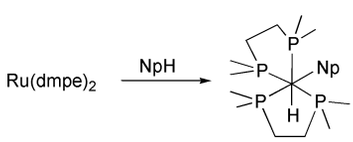
Stoichiometric alkane reactions

As early as 1965, Chatt[29] found cyclometalation[30] of CH bonds in a phosphine complex (eqn. (13))—essentially a CH oxidative addition driven by the chelate effect.



(13)

The Chatt system[29a] also gave intermolecular CH addition of an arene (eqn. (14); Np = 2-naphthyl), but not of alkanes. This



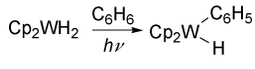
(14)

pattern of enhanced arene reactivity *versus* alkanes has proved general. At first sight this seems unexpected because arene CH bonds are far stronger than those of alkanes. The reason has been traced in part to the much stronger M–aryl *versus* M–alkyl bond strengths.[6] In many cases where arene addition is exothermic, the corresponding reaction for alkanes is believed to be endothermic. A kinetic factor is the less hindered character of an arene CH bond and the possibility of precoordination to the ring.[15]

Chatt considered that these results implied that alkane CH bonds should also be able to react if a suitable system were found.[29b] In 1968, Halpern[31] recognized the importance of the field by calling on chemists "...to develop a successful approach for the activation of CH bonds, particularly [in] saturated hydrocarbons, this problem being at present one of the most important and challenging in the whole field of homogeneous catalysis..." In spite of the great advances since that time, few new methods have since been found that are sufficiently powerful to find a regular place in the armory of the organic or industrial chemist. Much that seems eminently possible in principle is still unattainable in practice.

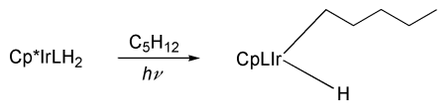
Cyclometalation represents an undesired side reaction in alkane activation chemistry, so a degree of resistance to cyclometalation is a useful feature in complexes intended for alkane reactions. Since steric bulk can help drive cyclometalation,[32] the presence of a relatively unhindered ligand set is desirable.

Photoextrusion of H_2 from dihydrides, found by Green[33] for Cp_2WH_2, gives a transient Cp_2W species that attacks the solvent *via* CH oxidative addition to give $Cp_2W(Ph)H$ (eqn. (15)); alkanes were unreactive, however.



(15)

In a major result by Bergman (1982),[34] direct formation of an alkylmetal species from a simple alkane proved possible by oxidative addition to give alkylmetal hydrides (eqn. (16)).



(16)

Photoextrusion of H_2 from $[Cp^*IrH_2(PMe_3)]$ led to an Ir(I) species that attacks alkanes with remarkably low activation energy. By using the photon energy, a highly reactive intermediate became accessible. The important lesson from this work is that the oxidative addition product is observable.

The groups of Graham[35] and of Jones[36] provided important evidence of generality with parallel examples in the same period and many related cases have now been found.[37]

The reactive intermediate is also accessible thermally, as Bergman[34] showed with the establishment of the equilibrium between the cyclohexyl hydride and *n*-pentane at 140 °C.

The equilibrium constant of 10.6 translates to a thermodynamic preference of *ca.* 5.5 kcal mol^{-1} for the Ir–pentyl over the Ir–cyclohexyl bond. The thermal reaction was also successful for methane, giving the methyl hydride in moderate yield. Cyclooctane was used as an inert solvent for the methane reaction because it was among the least reactive alkanes.

This work led to a reappraisal of the thermodynamics of M–C and M–H bonds. These had been previously thought to be uniformly rather weak and insufficient to make alkane oxidative addition possible. In fact they, like other M–L bonds in transition metal chemistry, tend to be variable in strength—much more so than bond energies in organic chemistry—and heavily influenced by the nature of the metal and coligands and by steric effects.[38]

The mechanism of the reaction has been studied in great detail.[39] Ultrafast kinetics studies on $Tp^*M(CO)_2$ (Tp^* = tris(2,4-dimethylpyrazolyl)borate; M = Rh, Ir) show the initial photoprocess is CO loss to give (η^3-Tp*)M(CO), which forms an alkane adduct in a few ps without CH bond cleavage. Over 200 ps, one arm of the chelate ligand decoordinates to give the square planar (η^2-Tp*)M(CO)(alkane). This undergoes oxidative addition over 230 ns, followed by rechelation of the Tp* over 200 ns to give the final product, (η^3-Tp*)M(CO)(R)(H). Similar studies on $CpIr(CO)_2$ in cyclohexane, excited at 267 nm, were interpreted in terms of photoextrusion of CO with an 18% quantum yield to give solvated CpIr(CO), which in turn gives CH activation with a very short 2 ps timescale, consistent with the almost barrier-free process predicted in theoretical work.[40] The remaining 80% of the photoexcited molecules relax *via* non-dissociative pathways.

Activation has proved much easier than functionalization in such systems, but Hartwig[41] has tried to remedy this problem by arranging for the metal fragment that activates the alkane also to carry a ligand, X, capable of reductive elimination with the alkane-derived alkyl, R, to form RX. This ligand X has to be thermally and photochemically stable to avoid scission of the M–X bond to give X radicals. Any such radicals could abstract H atoms from the alkane with radical selectivity, however, so this pathway would be readily distinguishable. Few ligands X qualify in terms of stability of the M–X bond, but stoichiometric borylation of alkanes is possible using metal boryl reagents such as $Cp^*W(CO)_2$(Bcat′) (cat′ = 3,5-dimethylcatecholate) under photolysis, where X is Bcat′. The unusual 3,5-dimethyl substitution pattern was required to prevent the metal attacking CH bonds of the catecholate group. The high terminal selectivity again indicates an oxidative addition mechanism operates: *n*-pentane gave the linear C_5H_{11}Bcat' species as the only functionalization product in 85% yield. The mechanism proposed involves photoexpulsion of CO, oxidative addition of alkane to the 16e intermediate, followed by reductive elimination to form the alkylboronate ester product.

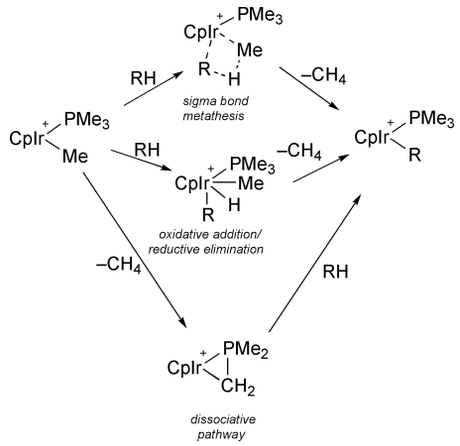


Fig. 1 Organometallic CH activation pathways.

Activation has also proved possible *via* sigma bond metathesis (Fig. 1), usually with early metal compounds. A typical example[42] is shown in eqn. (17).

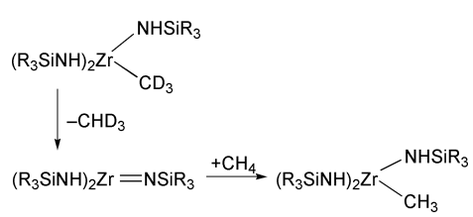
$$Cp^*_2LuCH_3 + {}^{13}CH_4 \rightleftharpoons Cp^*_2Lu{}^{13}CH_3 + CH_4 \quad (17)$$

Here, oxidative addition is not required. Instead, an alkane complex forms, followed by proton transfer between RH and R within the coordination sphere of the metal. This relies on the acidification induced in the alkane on binding, together with the anionic character of the alkyl in an early, electropositive metal. The best studied example is shown in eqn. (18).[43]

$$[Cp^*IrL(CH_3)]^+ + RH = [Cp^*IrL(R)]^+ + CH_3H \quad (18)$$
$$[L = PMe_3]$$

The mechanism of eqn. (18) has been controversial. Sigma bond metathesis[16,44] (Fig. 1), common for early metals, may play a role in these late metal systems but in such cases it is hard to distinguish from other pathways such as oxidative addition. Of the two possibilities, Hall and co-workers[45] implicated the oxidative addition/reductive elimination path by DFT calculations, but on the basis of mass spectral work, Plattner, Chen and Hinderling[46] prefer an entirely different, dissociative pathway for $[CpIrLMe]^+$.

A reaction involving H_3C–H addition across a Zr=N double bond may also involve a methane complex as intermediate. The imide is formed by thermolytic loss of CD_3H as shown in eqn. (19).[47]



(19)

Stoichiometric dehydrogenation

We argued[6,48] that since alkenes can be hydrogenated to alkanes by homogeneous transition metal catalysts and the catalyst must in principle mediate both the forward and reverse reactions, alkane conversion *via* dehydrogenation should be possible. To provide a driving force for what would normally be an endothermic process, we hoped to look for dehydrogenation activity using cyclopentane. We expected this to be converted to cyclopentadienyl, where the large binding energy should be enough to drive the reaction. An iridium complex proved best suited to these reactions and additional driving force was provided by using *t*-BuCH=CH_2 as hydrogen acceptor, because its heat of hydrogenation is particularly high.

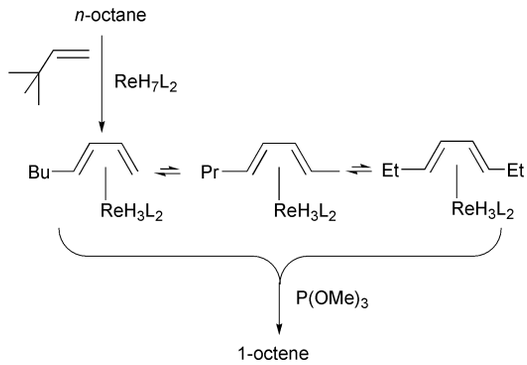


Fig. 2 Selective stoichiometric formation of 1-octene from *n*-octane.

$$[IrH_2(S)_2L_2]^+ + C_5H_{10} + 3t\text{-BuCH=CH}_2 =$$
$$[(C_5H_5)IrHL_2]^+ + 3t\text{-BuCH}_2\text{–CH}_3 \quad (20)$$

Felkin and co-workers[49] found a series of active complexes and with $ReH_7(PPh_3)_2$ succeeded in dehydrogenating linear alkanes to diene complexes. For *n*-octane, a series of interconverting isomers was formed. Remarkably, addition of $P(OMe)_3$ led to specific release of 1-octene, the least stable but most desirable alkene isomer (Fig. 2).

$[Cp^*Ru(NCMe)_3]^+$ gave dehydrogenation of cyclohexane to an arene complex, with photochemical activation of the complex causing dissociation of the MeCN ligands.[50]

Metalloradical reactions

Rhodium porphyrins form Rh–Rh bonded dimers that reversibly dissociate to give the monomeric Rh(II) radicals. These can activate methane *via* eqn. (21).[51] A termolecular step in the mechanism would be avoided if methane formed an adduct with the monomer that was intercepted by the second molecule of metalloradical, although evidence for this is lacking.

$$[RhL]_2 \rightleftharpoons 2RhL \xrightarrow{CH_4} CH_3RhL + HRhL \quad (21)$$

Catalytic alkane reactions

These divide into four general types. The most versatile and extensively studied are the Shilov catalysts. These involve Pt(II) and related metals, usually in aqueous or polar solvents. The products formed from the alkane, RH, are of the general type RX, where X can be D, a halide or an OH or, in the Periana version, an OSO_3^- substituent. Next come alkane dehydrogenation catalysts, where an alkene, diene or arene can be formed. Alkane carbonylation catalysts are also known. Finally, catalytic alkane borylation has recently proved possible.

Shilov and related chemistry

The classic Shilov system[5] is perhaps the most important of all alkane oxidation catalysts. The proposed pathways involve the formation of direct metal–carbon bonds, hence the assignment to the organometallic class. Garnett and Hodges[52] had shown that Pt(II) salts in aqueous CH_3COOD are able to effect H/D exchange in arenes. Exchange was even found at all three positions along the *n*-propyl side chain of $PhCH_2CH_2CH_3$, terminal exchange being preferred.[53] Soon afterwards, Shilov et al.[54] found that these conditions also cause H/D exchange in alkanes. The system showed a number of remarkable features. First, the selectivity tended to favor exchange at terminal CH_3 groups rather than the preferential attack at tertiary or benzylic CH bonds, as seen for electrophiles and radicals. This implied a new mechanism was involved and gave hope for potential

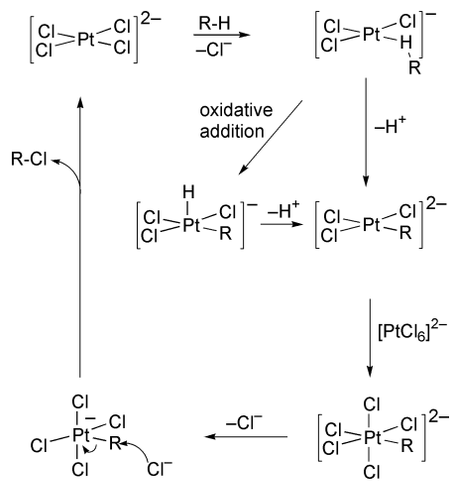


Fig. 3 A proposed mechanism for the Shilov reaction.

practical application, although rates were low. Second, multiple exchange was seen at the earliest stage of the reaction, even for CH_4.

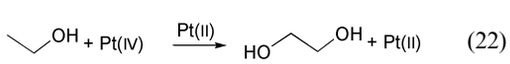
Incorporating platinum(IV) salts as primary oxidant allowed conversion of alkanes to alkyl chlorides or alcohols, albeit with modest rates and conversions.[55] The selectivity for terminal functionalization was essentially the same as earlier seen for the H/D exchange so it was concluded that conversion of Pt(IV) to Pt(II) oxidised the same intermediates responsible for H/D exchange. The selectivity pattern argues against an electrophilic attack of Pt on a CH bond, as does the kinetic analysis that identifies $[PtCl_2(solv)_2]$ as the most active species in the series $[PtCl_n(solv)_{4-n}]^{(2-n)+}$, with the $n = 0$ and 4 species being essentially inactive.

Cyclic alkanes were converted to arenes by the same system as a result of HX elimination from the functionalized cyclohexane intermediates and subsequent functionalization of the alkene intermediates.[5]

In an important step, Shilov showed that a methylplatinum(IV) intermediate, $[MePtCl_5]^{2-}$, could be directly detected in the reaction mixture from methane, strongly suggesting that metal alkyls are intermediates. Two books are the best source for detailed information on this chemistry.[5b,c]

Even though these results were mostly either ignored or met with disbelief at first, they can now be seen as the origin of the organometallic class of alkane oxidations. Together with Chatt's work on cyclometalation, they were a strong influence on my own work on C–H activation from 1978.

Labinger and Bercaw[56] have gone far in trying to understand the Pt system. The unusual selectivity is seen in one particularly striking experiment, where the tendency for attack at the terminal position of an alkyl chain is so strong that ethanol can be converted—at least in part—to ethylene glycol (eqn. (22)) in



(22)

spite of the fact that oxidants are normally highly selective for oxidation at the CH_2 group α to oxygen to give acetaldehyde or acetic acid.

The mechanism that results from all the work to date, shown in Fig. 3, involves initial interaction of methane with Pt(II) to give a methane complex. There is full agreement that a Pt(II) methyl is formed next, but it is not yet known if this occurs by oxidative addition followed by deprotonation or a direct deprotonation of the alkane complex. The reaction may follow both pathways or only one, because the barriers for each are believed to be very close in energy.[57] The Pt(II) methyl is rapidly oxidized by Pt(IV) *via* an electron transfer, not an alkyl transfer, to give Shilov's methylplatinum(IV) intermediate, $[MePtCl_5]^{2-}$. This rapidly undergoes an S_N2 nucleophilic attack by Cl^- or water to give the product RCl or ROH. Ethane also gives functionalized products rather than undergo β-elimination to give ethylene. This may be a result of the Cl^- *trans* to the high *trans* effect alkyl group being easily lost. This produces a five-coordinate intermediate with an empty site *trans* to the alkyl, which makes it unsuitable for β-elimination. The square planar $[PtCl_4]^{2-}$ fragment then becomes an excellent leaving group, encouraging nucleophilic attack by Cl^- or H_2O on the alkyl to give the final product.[58]

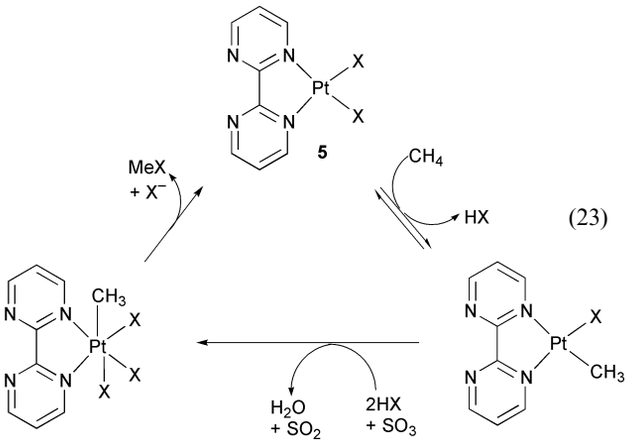
The problem with the Shilov system from a practical point of view is that Pt(IV) is not an economically viable stoichiometric oxidant. Efforts to replace the Pt(IV) were complicated by the fact that the alkane interacts only with the Pt(II) catalyst, also present, but most primary oxidants tend to convert reactive Pt(II) to catalytically inactive Pt(IV). In the 1990s, however, Periana[59] at Catalytica Corp showed that concentrated sulfuric acid can act as a selective oxidant for the key methylplatinum(II) intermediate and developed two related conversions of methane to the methanol derivative, CH_3OSO_3H. The first employed Hg(II) as catalyst and the second a bipyrimidine complex of Pt(II); both used sulfuric acid as solvent. The key advantage of this approach is that the final product, CH_3OSO_3H, proved to be highly oxidation-resistant as a result of the electron withdrawing character of the sulfonate group.

In the mercury case, the reactive 'soft' Hg(II) ion has the highest accessible oxidation state, so it can coexist with oxidants. The limitation in this case is that unlike Pt(II), Hg(II) cannot be readily modified by altering the ligand set in the hope of increasing the rate. In the absence of oxidative addition as a possibility, the reaction is believed to go with deprotonation of an alkane complex as the step that forms MeHg(II) ion, observed as an intermediate in the catalytic medium. Nucleophilic attack by bisulfate ion gives methylbisulfate with release of Hg(0) as leaving group. This Hg(0) is trapped by Hg^{2+} to give Hg_2^{2+}, which is then oxidized by the sulfuric acid to regenerate Hg(II). Together with O_2, the SO_2 resulting from reduction of the sulfuric acid is the starting material in commercial sulfuric acid synthesis. This gives a way in which O_2 could become the primary oxidant for methane in any eventual Catalytica process. Practical difficulties have so far prevented commercial implementation, however.

For the platinum case,[59b] change of ligands was explored as a way to improve the catalyst. However, few ligands survived the strong acid conditions of the Catalytica work or gave an improvement over the original Shilov Pt system. 2,2′-Dipyrimidine is the exception—this binds Pt(II) so effectively in **5** that it inhibits parasitic oxidation to Pt(IV) and, more remarkably, resists decomplexation from the metal even in concentrated sulfuric acid. Protonation of the uncomplexed nitrogen atoms may also be a factor in the success of this system. A novel aspect of this system is that nitrogen ligands are still not very widely used as stabilizing ligands in organometallic chemistry. Again, nucleophilic attack of an intermediate alkyl by HSO_3^- is believed to lead to the $MeOSO_3^-$ product (eqn. (23)).

A feature of these and several alkane conversion catalysts is the presence of strong acid—presumably required to protonate any potentially ligating bases that might otherwise compete with alkane to bind at the metal. Since methane itself does not protonate with acids like H_2SO_4 the ligating power of the substrate alkane is unaffected in acid.

The Periana systems favor terminal methyl attack and show organometallic selectivity, but the reaction is a hydroxylation and the primary oxidant is air or O_2, as in the coordination chemistry approach. This combination is very attractive and provides what is currently the most promising new approach to practical alkane conversion.



(23)

Syngas processes

In spite of much effort, no practical direct catalytic oxidation of methane to methanol has proved economically viable. Until a direct oxidation becomes available, processes have been commercialised that start with thermal conversion of CH_4/O_2 to 'syngas' (H_2 + CO).[60] A water gas shift (eqn. (25)) is sometimes needed to alter the H_2/CO ratio and the steps of eqns. (24–25)

$$CH_4 + ½O_2 \rightleftharpoons 2H_2 + CO \quad (24)$$

$$H_2O + CO \rightleftharpoons H_2 + CO_2 \quad (25)$$

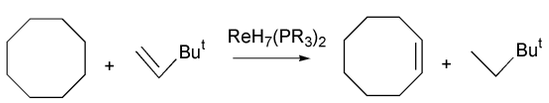
$$2H_2 + CO = CH_3OH \quad (26)$$

can be combined. This is followed by conversion of the syngas either to methanol with an acidic Zeolite catalyst, or to linear hydrocarbons with a Fischer–Tropsch catalyst. The latter is inelegant chemically because the methane is first overoxidized to the CO level and then has to be reduced to the final products, with formation of water as undesired waste product. The engineering of both processes is very sophisticated, however, and their economics will be hard to beat.

$$(2n + 1)H_2 + nCO = H\{CH_2\}_nH + nH_2O \quad (27)$$

Alkane dehydrogenation

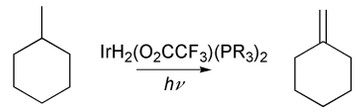
Following their work in stoichiometric dehydrogenation, Felkin and co-workers[49] showed that their neutral rhenium compound could release free alkene, allowing authentic catalytic dehydrogenation (eqn. (28)). Cyclooctane, one of the worst



(28)

substrates for oxidative addition in the Cp*IrL system, is one of the best substrates for dehydrogenation. The transannular H···H repulsions of the tub conformation destabilize the alkane relative to the alkene, where half of these interactions are absent, and give it a heat of dehydrogenation (23.3 kcal mol^{-1}) 5–7 kcal mol^{-1} lower than most alkenes. Our *t*-BuCH=CH_2 was again used as hydrogen acceptor, making the reaction a transfer hydrogenation (eqn. (28)).

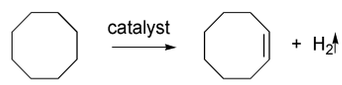
Moving to a neutral catalyst, $[IrH_2(PAr_3)_2(OOCCF_3)]$, gave us[61] not only thermal, but also photochemical dehydrogenation. Eqn. (29) illustrates the selectivity for attack at the exocyclic methyl group, which gives methylenecyclohexane after β-elimination. Since this is the least stable alkene that can be formed from methylcyclohexane, it is certainly a kinetic product. Photodehydrogenation does not require a hydrogen acceptor because the photon energy drives the reaction. It is



(29)

also carried out at room temperature, where alkene isomerization is very slow, so the initial non-thermodynamic alkene product isomer ratio is retained during the reaction.

One other procedure also allows the reaction to be driven without use of a hydrogen acceptor. Saito[62] showed that thermal alkane dehydrogenation, with reflux of a high boiling solvent, causes the hydrogen to be driven from the system, allowing build-up of the alkene product (eqn. (30)). These acceptorless conditions were also successfully applied to other catalysts.[63]

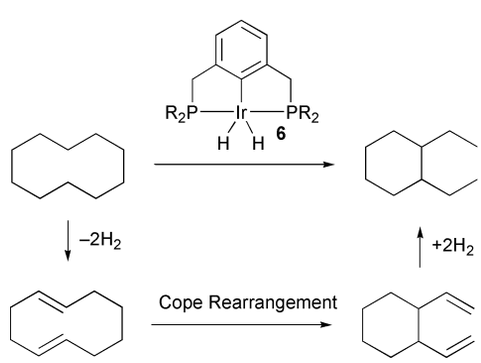


(30)

Thermal stability of the catalyst was a severe limitation in these early systems. For example, the activity of the $[IrH_2(PAr_3)_2(OOCCF_3)]$ system was shown to decrease with the build-up of ArH, a material formed by P–C bond cleavage in the PAr_3 ligand. Accordingly, an important theme in the 1990s has been increasing the catalyst lifetime. PMe_3 has received attention as a ligand less likely to degrade. In particular, $[RhCl(CO)(PMe_3)_2]$ has proved very efficient in photodehydrogenation.[64] Counter-intuitively, it works best in a hydrogen atmosphere, so the norbornene hydrogen acceptor is also directly hydrogenated during the reaction. Other precursors to '$RhClL_2$', the active species, are also effective.[65]

At 170 °C, the ethylene complex, $[RhCl(C_2H_4)(PMe_3)_2]$, catalyzes alkane dehydrogenation with ethylene as hydrogen acceptor. At 230 °C, ethylene insertion into the alkane CH bonds is seen. The catalyst's survival at these high temperatures is a testament to the thermal robustness of PMe_3.[66]

An interesting development[8] is the use of the thermally very stable pincer phosphines (**6**; R = *t*-Bu, *i*-Pr) to give catalysts of very high stability and activity. The conformational constraints of the pincer system prevent degradation by limiting access by the metal to the potentially labile P–C and C–H bonds of the ligands. Shaw[67] had shown that these ligands give very stable complexes that can even be sublimed at >250 °C. Iridium pincer complexes have proved very active and stable, with a dehydrogenation rate of 12 turnovers min^{-1} for cyclooctane at 200 °C.[8] They are also suitable for acceptorless conditions: total turnovers of nearly 1000 mol (mol catalyst)$^{-1}$ have been observed in this way. Cyclodecane can give 1,2-diethylcyclohexane as a result of dehydrogenation to the diene, followed by a Cope rearrangement and rapid hydrogenation (eqn. (31)).[68] At these high temperatures, the dehydrogenation



(31)

equilibrium lies sufficiently over to the alkene that significant amounts of alkene are formed at equilibrium even without a hydrogen acceptor.[69]

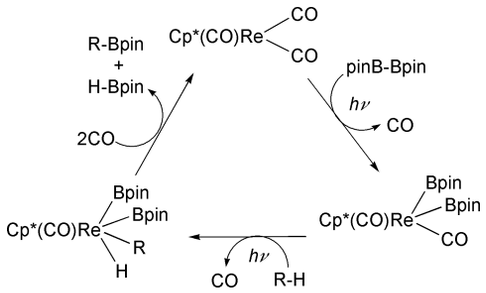


Fig. 4 A proposed mechanism for photochemical alkane borylation.

Niu and Hall[70] have analyzed the pincer iridium catalyst $[LIrH_2]$ (**6**) with DFT theoretical methods. Alkane oxidative to give an Ir(v) species $[LIrRH_3]$ is followed by reductive elimination of H_2, β-elimination of the resulting [LIrRH] to give $[LIr(alkene)H_2]$ and then loss of alkene.

Cycloalkane dehydrogenation to arene, previously only stoichiometric,[52,71] becomes catalytic with pincer catalysts at 200 °C; cyclohexane gives cyclohexene and benzene and thf gives dihydrofurans and furan, for example.[8]

Alkane carbonylation

Alkane carbonylation, which can be thought of as the reverse of aldehyde decarbonylation, also proved to be possible in a number of cases using $[RhCl(CO)(PMe_3)_2]$ as catalyst and photolysis to drive this endothermic reaction. The same selectivity pattern of preferential attack at a terminal methyl group is also apparent in this work, suggesting that initial CH oxidative addition occurs, as is indeed expected if the reaction is the mechanistic reverse of aldehyde carbonylation.[72] Since the same catalyst is effective in alkane photodehydrogenation, alkene is also formed in most cases.

$$R–H + CO = RCHO \qquad (32)$$

Alkane borylation

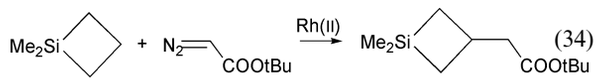
Hartwig[73] has extended the stoichiometric borylation, discussed above, to catalytic applications. In the photochemical version, the reaction of eqn. (33) is light-driven. The proposed mechanism (Fig. 4) involves two photoexpulsions of CO, presumably implicating two photons, to allow a double oxidative addition of the two reagents. Reductive elimination can then give the two products. Thermal alkane borylation is founded on the premise that eqn. (33) is exothermic.[74]

$$R'_2B–BR'_2 + R–H \rightleftharpoons R'_2B–R + H–BR'_2 \qquad (33)$$

The thermodynamics, in part predicted *via* computational work, is favorable because the appropriate bond energies for the reagents are less than those for the products: B–B, 104 and C–H, 98 *versus* B–C, 112 and B–H, 111 kcal mol^{-1} The best catalyst, $[CpRh(C_2H_4)_2]$, at 150 °C and 5 mol% loading, gave 85% exclusively of (1-octyl)B(pin) from *n*-octane (pin = pinacolyl). The mechanism remains to be clarified, but double oxidative addition in direct analogy with the earlier proposal of Fig. 4 is unlikely for Rh(I).

Metal catalyzed carbene CH insertion reactions

Rh(II) complexes, such as $Rh_2(OCR)_4$, catalyze the decomposition of diazoalkanes and the insertion of the resulting carbenes into unactivated CH bonds. This most often happens with chelate assistance and control of selectivity, although the intermolecular example of eqn. (34) is an exception. These reactions can be carried out with asymmetric induction using a chiral ligand and have proved very useful in organic synthesis.[75]



(34)

Gas phase chemistry

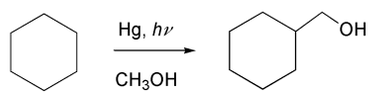
Naked metal ions react readily with alkanes in the gas phase, yielding C–H and C–C bond breaking reactions. The ion reactions are often studied by mass spectroscopic methods,[76] Both CH and CC bond breaking reactions occur readily. For example, Ni^+ reacts with *n*-butane to give $[Ni(C_4H_8)]^+$ and H_2, $[Ni(C_3H_6)]^+$ and CH_4, and $[Ni(C_2H_4)]^+$ and C_2H_6.[77] Pt^+ reacts with methane to give $[Pt(CH_2)]^+$ and H_2.[78]

Naked metal atoms can also react under metal vapor synthesis conditions (*e.g.*, eqn. (35)),[79] where photoexcitation of the

$$W + C_5H_{10} + PMe_3 = (C_5H_5)WH_5(PMe_3) \qquad (35)$$

atoms by the attendant light emission cannot be eliminated as a factor in promoting the reaction.

Metal atoms can be deliberately activated by photolysis, as in the well-known mercury photosensitized reactions, where an excited state metal atom abstracts an H atom from the alkane (eqn. (36)). The final products are formed by radical recombin-



(36)

ation or trapping, depending on the co-reagents present and conditions. The Hg reactions have been made preparatively useful on a multigram scale by using a reflux reactor; in this case, selectivity for radical recombination or trapping products can be strongly enhanced because the recombination product condenses and is protected from further conversion and because the radical disproportionation products, alkene and alkane, are volatile and are converted back to the key intermediate alkyl radicals.[80]

Theory has been very valuable in CH activation,[81] and is most clearly needed for studying metal ion chemistry, where mechanistic studies are difficult to carry out. For example, Goddard[82] studied eqn. (37), finding an exothermicity of only 3

$$Ir^+ + CH_4 = [Ir{=}CH_2]^+ + H_2 \qquad (37)$$

kcal mol^{-1}. Since eqn. (38) [the ^{3} refers to triplet CH_2] has an

$$CH_4 = {}^3CH_2 + H_2 \qquad (38)$$

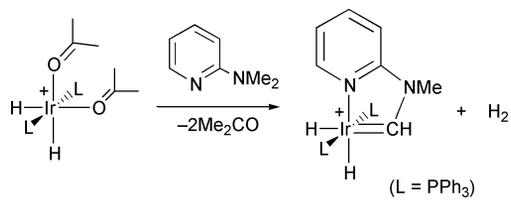
endothermicity of >110 kcal mol^{-1}, this means[83] the metal must stabilize the carbene by this amount. The Rh^+ reaction is barrier free, apart from the endothermicity.[84]

The mechanism in the Ir case is predicted to go *via* an $[Ir(\eta^2\text{-}CH_4)]^+$ complex (eqn. (39)) that gives an oxidative addition

$$Ir^+ + CH_4 = [Ir(\eta^2\text{-}CH_4)]^+ = [H–Ir–CH_3]^+ = [(H)_2Ir{=}CH_2]^+ = [(H_2)Ir{=}CH_2]^+ = [Ir{=}CH_2]^+ + H_2 \qquad (39)$$

followed by α-elimination and reductive elimination of H_2. The authors identify the features of Ir^+ that fit it specially well for carrying out this reaction: the ability to change spin state easily; the high M–H and M–C bond strengths; and the availability of the Ir(v) oxidation state, required at the $[(H)_2Ir{=}CH_2]^+$ stage. The latter is also the global minimum along the pathway.

The authors suggest that metal complexes might also give a similar reaction. Indeed, a chelate assisted version of the reaction is known (eqn. (40)),[85] but it requires additional stabilization of the carbene by an adjacent nitrogen to make the



(40)

reaction thermodynamically allowed, so the stabilizing effect of metal binding on the carbene is much lower for the full complex than for the bare metal ion.

The coordination chemistry approach

This approach[4,5c] has been very actively pursued in the last decade, not only because of the close relationship with biochemical oxidation, but also perhaps because the oxidants desirable for catalytic alkane conversion seem more compatible with coordination than organometallic compounds. Since alkane oxidising enzymes use air as oxidant, at first sight a coordination chemistry approach using enzyme model systems with air seems to have an important advantage for practical applications. As we see below, the need for a co-reductant together with air greatly complicates the issue.

The mechanisms, both of the enzymes and in model systems, have proved to be very difficult problems. The consensus mechanisms that survived the 1980s came under increasing pressure in the 1990s as new experimental facts came to light. New and much more complex ideas have now emerged but have still not settled into a new consensus. In what follows, we refer to the older mechanisms as 'classical' to distinguish them from the newer proposals.

Monooxygenase *versus* dioxygenase chemistry

When monooxygenases use O_2 to oxidise an organic substrate, say a C–H bond, two equivalents of reducing power must be supplied to the system either in the form of $2H^+ + 2e^-$, or equivalently, two hydrogen atoms. In nature, this reducing power comes from NADH or NADPH, cofactors common in cellular biochemistry but harder to duplicate or replace in model systems. If a monooxygenase enzyme itself were to be used for alkane oxidation, for example, either NADH would have to be supplied in stoichiometric quantities or a secondary catalytic cycle would be needed to regenerate it; even if this were done successfully, a primary reductant, such as H_2, would still be needed. The stoichiometric requirement for this primary reductant along with the O_2 severely affects the economics of alkane oxidation by this pathway.

In model systems, a reductant is often present along with O_2 for the same reason. In both biomimetic and enzyme systems that operate by a monooxygenase pathway, one of the two O atoms of O_2 is reduced to water by the two reducing equivalents and the second is converted to a powerful oxidant, such as a metal oxo group that can hydroxylate the alkane. Consequently, if labeled O_2 is used, half the label appears in the oxidised substrate and half is eliminated as water.

$$O_2 + 2H^+ + 2e^- + C\text{–}H = H_2O + C\text{–}O\text{–}H \qquad (41)$$

In cytochrome P450,[4] a typical monooxygenase that hydroxylates unactivated CH bonds, the iron–porphyrin cofactor has a thiolate axial ligand; in model systems thiolate ligands do not normally survive the oxidizing conditions and are replaced in models by ligands such as pyridine. This leaves the sixth coordination site of the heme open to bind O_2 at the Fe(II) level to give an Fe(III) superoxide. This is reduced by NADPH to an Fe(III)–OOH species that in the classical mechanism loses H_2O *via* heterolysis of the O–O bond to give an Fe(V) oxo active form.

One way of avoiding the need for this external reductant is to avoid the 4e oxidant, O_2, by moving to two-electron oxidants such as peroxides or oxo transfer agents, such as PhIO. This 'shunt' approach is common in both enzyme and model systems but it cannot conceal the fundamental requirement for an O_2 reduction step at some point, whether it precedes or accompanies the alkane oxidation. The economic consequences are not so severe in the peroxide case because peroxides, particularly H_2O_2, are much easier to obtain at relatively modest cost.

Dioxygenase pathways that use both O atoms of O_2 for incorporation into substrate do exist but they normally only operate for substrates that are much easier to oxidise than alkanes and so are less relevant here. An example is a lipoxygenase that can oxidise arachidonic acid by conversion of an allylic CH bond to a C–OOH group.[4]

Several books cover various aspects of metal-catalyzed alkane oxidation and enzyme modeling. This is now a wide field because a considerable number of enzymes, containing Fe, Cu or Mn, are known that hydroxylate CH bonds.[4,5,86,87]

Coordination compounds as catalysts

In spite of the difficulties, initial success in alkane oxidation *via* transition metal catalysis was achieved as early as 1898, when Fenton[88] reported that hydrogen peroxide and iron(II) salts can hydroxylate alkanes, but with poor conversion and yield. Fenton chemistry, also called Haber–Weiss chemistry, is believed to release $HO^\bullet$ radicals[89] by Fe-catalyzed decomposition of H_2O_2, *via* steps such as eqns. (42)–(44). These radicals

$$Fe(II) + H_2O_2 = Fe(III) + OH^- + {}^\bullet OH \qquad (42)$$

$$R\text{–}H + {}^\bullet OH = R^\bullet + H_2O \qquad (43)$$

$$R^\bullet + O_2 = R\text{–}O\text{–}O^\bullet \qquad (44)$$

then react with the alkane to form carbon radicals, making this an indirect mechanism by the definition discussed earlier. The HO–H bond dissociation energy (BDE) of 119 kcal mol^{-1} easily allows $HO^\bullet$ to abstract an H atom from an sp^3 C–H bond (typical BDE range 90–105 kcal mol^{-1}).

The $ROO^\bullet$ radical of eqn. (44) then goes on to give the observed products, such as alcohol and ketone. The Fe(III) is recycled by oxidation with H_2O_2.

Because of the possible relation of model oxidation chemistry to metalloenzyme alkane oxidation, this early work led to a series of biomimetic and bioinorganic catalysts. A classic early example of this type was Udenfriend's Fe(II)EDTA (ethylenediaminetetraacetate)–ascorbate–O_2 system, dating from 1954.[90] This was shown to hydroxylate arenes by a monooxygenase pathway, using ascorbate as the reductant. The system was extended to alkane oxidation by Hamilton[91] who also proposed an iron oxo species as reactive intermediate. The selectivity (tert. CH > sec. CH) is compatible with radical intermediates or, equally, an iron oxo species behaving as an H atom abstractor. Many improved versions were later reported.[5c] Mechanistic issues remain unresolved for these systems, however, and covert radical pathways remain a possibility.

A large number of proposed models for the ubiquitous cytochrome P450 dependent enzymes have been studied and this work has been extensively reviewed, notably by Groves[92] and Meunier.[93a] A variety of Fe and Mn porphyrin complexes are able to model the enzyme reactions *in vitro* using the O atom transfer reagent, iodosylbenzene (PhIO), as the primary oxidant. In this work, what are believed to be the key iron oxo intermediates were directly detected and characterized: an Fe(IV) oxo species and an Fe(IV) oxo with an oxidized porphyrin ring making it a formally Fe(V) oxo species. The 'Fe(V)' species

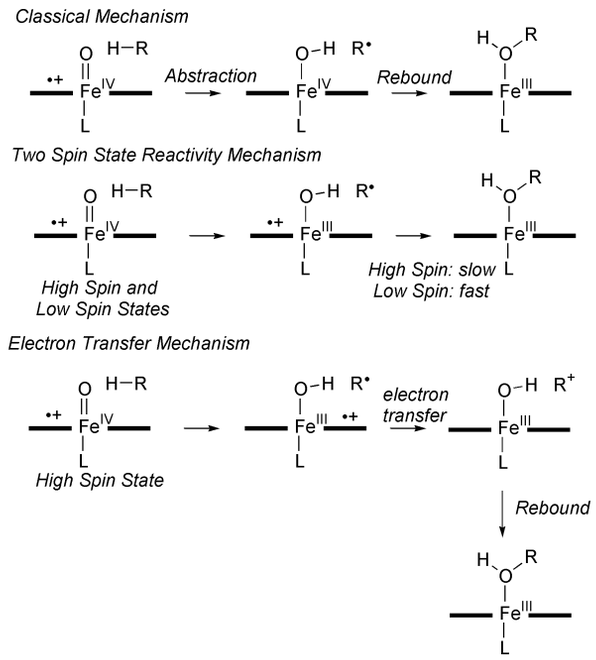


Fig. 5 Possible mechanisms for CH hydroxylation by P450 enzymes and their models.

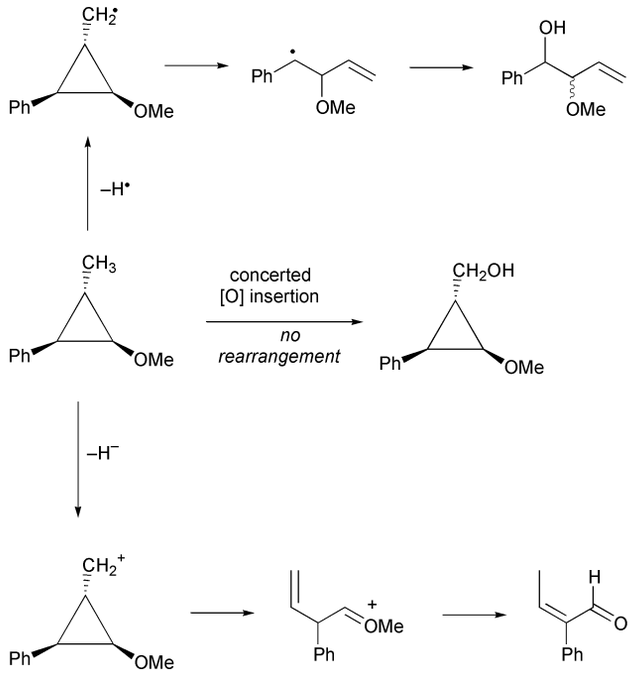


Fig. 6 Clock substrate rearrangements that distinguish radical from carbonium ion pathways.

was shown to hydroxylate alkanes and epoxidise alkenes and is believed to be a close model for the enzyme active form.[94,95]

Other primary oxidants have proved satisfactory in model work: Meunier[4,93a] introduced hypochlorite ion and monopersulfate, and Bruice,[93b] trialkylamine *N*-oxides, all efficient O atom donors to the metal to give metal oxo intermediates. Hydroperoxides (ROOH) seem less satisfactory because of the facile metal-induced O–O bond homolysis they can undergo; such a step can lead to undesired pathways *via* $RO^{\bullet}$ radicals.

The main features of the classical hydroxylation mechanism (Fig. 5) due to Groves[94] are as follows. Reduction of the Fe(III) form of the enzyme to the Fe(II) state is followed by O_2 binding to give an Fe(III)–superoxo complex, reminiscent of that in hemoglobin and myoglobin. A subsequent reduction step to a peroxo complex, Fe(III)–OOH leads to formation of the active oxidant and release of H_2O *via* O–O bond heterolysis. The resulting reactive 'Fe(V)' oxo is proposed to abstract an H atom from the alkane, RH, to give an 'Fe(IV)–OH' species in a cage with $R^{\bullet}$. The latter recombines with the Fe(IV)–OH, denoted the 'rebound' step, finally to give ROH and Fe(III). In line with this proposal, the pathway usually shows a substantial primary isotope effect ($k_H/k_D = 5$–13). The rebound (C–O bond forming) step must be fast (*ca.* 10^{10} M^{-1} s^{-1}) because there is often a moderate to high degree of retention of stereochemistry at carbon and the radical lifetimes are estimated using fast radical 'clock' rearrangements.[96] Only when the radical lifetime is longer than the half life of the clock rearrangement, should the rearranged final product predominate.

$$C–H + Fe{=}O \rightarrow Fe–OH + C^{\bullet} \quad (45)$$

$$Fe–OH + C^{\bullet} \rightarrow C–OH + Fe \quad (46)$$

During the 1990s, unexpected observations were made, however, that called the classical mechanism into doubt. For example, some radical clocks that normally rearrange fast nevertheless show less rearrangement than other slower clock radicals. Several possibilities were discussed to explain this finding,[97a] but doubt remained. Clock substrates that rearrange differently (Fig. 6) depending on whether a carbocation or a radical is formed were applied to the problem by Newcomb *et al.* with the striking result that the product of carbonium ion rearrangement was formed in significant amount. The conclusion that carbonium ions are involved seemed solid, but it was hard to see how they could be formed. Newcomb *et al.*, suggested OH insertion into RH from the Fe(III)–OOH intermediate.

A potential complication raised by Shaik and Schwartz[98a] and co-workers concerns the presence of distinct spin states for typical oxometal species. More than one such state could well be thermally accessible. These states are distinct spin isomers with (subtly) different structures, and they may, in principle, differ strongly in their reactivity and even have quite distinct reaction mechanisms. In the extreme, all the reaction could pass through a state that is a minor constituent of the spin state equilibrium, so biophysical measurements on an intermediate could be irrelevant to the true reaction pathway. Such spin state reactivity differences are not confined to iron, but have been proposed for Mn oxo intermediates implicated in O_2 evolution by Photosystem II.[99] Issues related to spin state are likely to become generally important for paramagnetic metal centers in biology. One point not yet understood is how the rate of spin state interconversion, not a well-known quantity either experimentally or theoretically for typical cases of interest, affects the outcome of such reactions. If interconversion is very fast, the reaction could all pass *via* the lowest transition state; if slower, the paths could operate entirely independently. This thorny problem could become a key issue in future work.

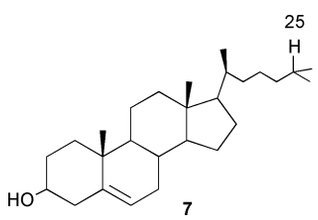
Shaik and co-workers[98b] went on to apply this line of thought to P450 itself, using theoretical methods (DFT). For the key abstraction and rebound steps, two spin states, doublet and quartet, were found relatively close in energy, implying that both could contribute to the observed reactivity of an 'Fe(V)' oxo intermediate (two spin state reactivity mechanism in Fig. 6). Both states were found to be able to abstract an H atom from the RH substrate with a transition state reminiscent of radical abstraction pathways. While the low spin doublet surface gave an essentially barrier-free rebound, so that the R radical could be said to have a vanishingly small lifetime, the high spin quartet surface had a significant barrier, leading to a non-zero radical lifetime. The barrier was traced to the necessity for internal transfer of an electron from one iron orbital to another only in the high spin case.

Because it is so fluxional, CH_5^+ is said to be a species without a structure.[100] Similarly, P450 could be an enzyme without a

mechanism if no single pathway can explain the data. A simple scheme suggested here starts from the two spin state reactivity model of Shaik *et al.* and proposes that the high spin radical pair of that scheme gives electron transfer with the adjacent porphyrin radical cation to form a carbonium ion that has a short lifetime before the rebound step traps it. This could give R^+ enough time to rearrange (Fig. 6).

Halogenation of the porphyrin makes the ring less sensitive to destructive oxidative degradation and thus improved the efficiency of the catalyst.[101] Elaborate cavities have been constructed in model heme systems to mimic the effects of the enzyme binding site; these can show strong shape selectivity effects.[92]

Several very elegant studies have involved creation of a binding pocket adjacent to the porphyrin, leading to selectivity being imposed by nature of the cavity or the binding of the substrate. Examples of groups that have been added in this way include, cyclodextrin cavities for steroid hydroxylation,[102] a chiral asymmetric vault for asymmetric hydroxylation,[103] a basket-shaped vault for shape selectivity and enantioselectivity,[104] and cholesterol-derived 'columns' for incorporating the porphyrin within a lipid bilayer vesicle to achieve shape selectivity.[105] The latter, for example, hydroxylated cholesterol (**7**) at the C-25 carbon. This is the tertiary CH bond that is most remote from the cholesterol OH group, because the OH is forced to remain at the surface of the bilayer in contact with the aqueous phase. The opposite end of the molecule is therefore brought into contact with the porphyrin active center.



7

A number of alkane-oxidizing enzymes contain iron, but no heme group. These non-heme iron proteins include methane monooxygenase, MMO, an enzyme responsible for conversion of methane to methanol in a variety of bacteria.[3] In part, because of the commercial significance of methane conversion, MMO has been the focus of intense interest. The hydroxylating subunit contains a di-iron oxo cluster at the active site that is implicated in the reaction with methane.

Barton's discovery of a series of catalysts, often designated Gif and GoAgg systems, referring to Gif-sur-Yvette, France, and Texas A&M {motto: Go Aggies!}, the successive locations of his laboratories.[106] These typically consist of iron salts, picolinic acid as ligand, and *t*-BuOOH, H_2O_2 or superoxide as primary oxidant, in pyridine–acetic acid as solvent. They hydroxylate and form ketone from alkanes. The most efficient GoAgg systems use peroxides such as H_2O_2 or *t*-BuOOH as primary oxidants. They seemed to provide a model system for the non-heme iron enzymes, just as Groves and others[92,93] had done for the heme enzymes.

Initially, radical reactions were considered unlikely from the sec./tert. CH selectivity and reaction of intermediate metal oxo species with RH was proposed, but after a long discussion on the nature of the mechanism, it now seems clear that many Gif and GoAgg systems do indeed involve predominant carbon radical pathways.[107] Key pieces of evidence include finding alkylpyridines as products, consistent with attack on the pyridine solvent by alkane-derived radicals. Alkyl chlorides are also formed, consistent with alkyl radical attack on Fe(III)–Cl. Low alcohol/ketone ratios in products from cyclohexane are consistent with radical autoxidation. Rearranged products are seen from 'clock' substrate hydrocarbons, such as *trans*-1,2-methylphenylcyclopropane, that give radicals that rearrange fast (3×10^{11} s^{-1}). To test if Gif/GoAgg products are formed *via* O–O homolysis, *t*-BuO–OH was replaced with $PhCH_2CMe_2O$–OH, which gives a radical, $PhCH_2CMe_2O^{\bullet}$, with a 5 ns lifetime, owing to ultrafast C–C scission *via* eqn. (47). No Gif products

$$PhCH_2CMe_2O^{\bullet} = PhCH_2^{\bullet} + Me_2CO \qquad (47)$$

were seen with this peroxide, at least under anaerobic conditions, implying that H atom abstraction from alkane by the much longer-lived *t*-BuO$^{\bullet}$ radical is the main pathway in *t*-BuOOH-dependent Gif systems. Since the mechanisms in the enzymes are still under active discussion[108] it is not yet sure what relation there is between Gif chemistry and the enzyme mechanism.

Other catalysts of types originally considered non-radical have also been reevaluated,[96c] but a few are still considered non-radical. Oxone ($O–OSO_3^{2-}$) with its polarized O–O bond, shows a higher tendency to undergo heterolysis and transfer oxo groups to the metal and avoid the O–O homolysis step that leads to radical pathways. Metal catalysis of alkane oxidations with this oxidant can occur *via* a predominant non-radical path, as suggested by the stereospecificity seen in the reaction with *cis versus trans* decalin.[109]

Very strong evidence for a non-radical route with H_2O_2 as primary oxidant was obtained by Que and co-workers for a tris(pyridylmethyl)amine complex of Fe(II), where stereospecificity was seen in the hydroxylation of *cis*- and *trans*-1,2-dimethylcyclohexane (radical epimerization rate: 10^9 s^{-1}) and the epoxidation of *cis*- and *trans*-2-hexene.[110a] On the other hand, *t*-BuOOH as oxidant gives radical chemistry. Most recently, $H_2{}^{18}O$ solvent has been shown to incorporate label into cyclohexanol formed by hydroxylation of cyclohexane with H_2O_2 and a closely related catalyst, $[Fe(pyCH_2NMeCH_2CH_2NMeCH_2py)(MeCN)]^{2+}$ (py = 2-pyridyl). This suggests that an Fe(V)=O is formed and then exchanges label with water before reaction with alkane *via* a rebound or related mechanism.[110b]

Because in solution they can react unselectively, radicals were once considered unlikely intermediates in enzyme chemistry. Many cases have now been clearly established, however.[4] Any enzyme-bound radical intermediate will not be free and so its reactivity can potentially be controlled by the enzyme. This also makes it difficult to interpret standard tests for radical pathways, developed for reactions in solution, when applied to enzymes. Nevertheless, there seems to be good evidence for short lived carbon radical intermediates in certain enzymes such as non-heme iron monooxygenases.[111]

More recently, a number of interesting diiron cluster compounds have been described as functional models of MMO.[112,113] The industrial relevance and future potential of biomimetic and enzyme oxidation has recently been reviewed.[114]

Hydrogen atom transfer

Mayer[115] has shown that in spite of being diamagnetic, permanganate can abstract H atoms from suitable hydrocarbons, such as toluene, to give carbon radicals that subsequently undergo further oxidation. In this net hydrogen atom transfer, one can consider that a proton is transferred to the basic oxo group, while an electron is simultaneously transferred to the high valent Mn center. The activation energy of the H transfer step follows the same trend seen for authentic O-centered radicals, such as HO$^{\bullet}$, RO$^{\bullet}$ and ROO$^{\bullet}$, and depends on the $\Delta H°$ of the hydrogen transfer. This type of H transfer to metal oxo groups may be relevant to other hydrocarbon oxidation reactions, including enzyme mechanisms.[116]

Spin state changes may play a role in metal oxo chemistry, as suggested in recent reports. For example, an unreactive oxo, M=O, may convert into a reactive oxyl, M–O, by intersystem crossing.[98,99]

Non-biomimetic coordination catalysts

One interesting series of catalysts is the polyoxometalate clusters of Hill,[117] such as $H_3PW_{12}O_{40}$. These carry out a number of oxidations *via* photochemically induced net H^- transfer to the metal. The intermediate carbonium ion is trapped by the MeCN solvent to give amides after hydrolysis. These clusters are believed to model the behavior of semiconductor surfaces.

Some metal-catalyzed CH oxidation reactions have commercial utility. Various metal complexes, notably Co(III) carboxylates, when used with bromide ion as cocatalyst, promote the autoxidation of alkanes and other hydrocarbons by catalyzing the breakdown of the intermediate alkyl (or aralkyl) hydroperoxides. Br atoms, formed from oxidation of Br^-, are believed to play the role of radical chain carriers and lead to improved selectivity for benzylic and tert. CH bonds since $Br^\bullet$ is a weak H atom abstractor. Toluene conversion to benzaldehyde *via* this pathway is commercially viable.[118]

Cobalt(II) naphthanoate catalyses the radical chain autoxidation of cyclohexane to cyclohexanol and cyclohexanone; further treatment with HNO_3 gives adipic acid, a nylon precursor.[119]

Other pathways for alkane conversion

Many alkane reactions have been reported where a transition metal is either absent or plays an inessential role. Shilov and Shul'pin's book gives a detailed review and we only briefly mention some of these areas here.[5c] For example, as shown by Olah,[7] superacids are capable of protonating alkanes to give carbenium ions and H_2; the carbenium ions can then undergo any of a number of rearrangements or react with functionalizing reagents such as CO, as in the Koch–Haaf reaction (eqn. (48)).[120]

$$t\text{-Bu–H} + \text{CO} \xrightarrow{\{\text{superacid/CO}\}} t\text{-Bu–CHO} \qquad (48)$$

This chemistry forms the basis of several commercial alkane conversion reactions which often take place over solid superacids such as zeolites.

There is also an extremely extensive chemistry of alkanes over heterogeneous metal and metal oxide surfaces, giving cracking, isomerization, dehydrogenation, dehydrocyclization, alkylation, oxidative coupling and oxidation, again with broad commercial importance or potential.[5c]

Sen has reported a number of interesting systems for alkane functionalization in protic media, using a variety of oxidants, such as $S_2O_8^{2-}$ and Ce(IV).[121] Conversion of methane to acetic acid with CO/O_2 and a $RhCl_3$ catalyst in aqueous perfluorobutyric acid is reported.[122] A number of other methane carbonylation systems have also been described.[123]

Future developments

The problem of alkane activation and functionalization by homogeneous transition metal reagents and catalysts will continue to attract attention. So far, the organometallic approach of Shilov and of Periana has come closest to producing a practical system. This may be because these combine a direct organometallic reaction pathway with an oxidation-resistant ligand set, more typical of coordination chemistry. Indeed, the main limitation of other organometallic approaches has been the failure of the current ligand sets to produce a stable, robust, highly active catalyst. With the current interest in expanding the range of ligands for catalysts beyond phosphines to nitrogen and carbon based ligands, we may expect to see a change. In particular, N-heterocyclic carbenes seem to be oxidation-resistant and could provide a basis for advance.[124]

In the coordination chemistry area, we would like to have better control over the formation of metal oxo groups and have an understanding of what factors affect their reactivity. There are already clues from experimental and theoretical work[98] that the spin state of the oxo is a key issue. Certain states can have O-radical character and these may be exceptionally reactive for H atom abstraction from the CH bond.

Another potentially useful approach is purely bioinorganic, using enzymes. Even if H atom transfer is involved, selectivity can be modulated by the enzyme, which can bind the substrate in such a way that only certain CH bonds are presented to the active site for cleavage. Desirable selectivity can therefore be obtained even when the chemistry involved would not have such selectivity in free solution. It should therefore be possible to modify alkane oxidising enzymes to allow them to attack alkanes with unnatural, designed selectivities.[4,93] This area is still little developed and practical exploitation lies in the future. One problem is that to date, alkane oxidising enzymes have been monooxygenases, rather than dioxygenases, a distinction that may make them hard to apply on a commercial scale.

The mechanisms of CH activation reactions such as the Shilov system and MMO and the P450 enzymes have proved extremely challenging and these and others will no doubt provide many more suprises in future. Development of an economically viable CH activation system for alkanes remains a major unsolved problem for the new millennium.

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