Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Molecular Catalysis A: Chemical 220 (2004) 27–35
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Selective alkane oxidation: hot and cold approaches to a hot problem

Jay A. Labinger*

Beckman Institute, California Institute of Technology, 139-74 Pasadena, CA 91125, USA

Received 19 January 2004; accepted 10 March 2004

Abstract

A large number of attempts at the selective oxidation of alkanes may be classified into three basic types: high-temperature heterogeneous catalysis, biological/biomimetic catalysis, and organometallic activation. In this essay I discuss mechanistic similarities and differences between the three approaches, and their implications for the best opportunities for achieving desired selective transformations.

Keywords: Alkane oxidation; Selectivity; Free radicals; Biomimetic oxidation; Organometallic activation

1. Introduction

The potential benefits of developing an armamentarium for the selective conversion of alkanes—readily available, relatively low-cost feedstocks—to more valuable oxidized products—unsaturated hydrocarbons as well as oxygenates such as alcohols, aldehydes, carboxylic acids and derivatives—do not need to be spelled out for readers of this issue. This is truly a hot problem. However, one can readily see that solving it presents formidable technical challenges. These have become increasingly evident over at least two decades of feverish activity, in industrial and academic laboratories around the world.

During this period I have been actively involved in a number of research projects in this field, in different venues, with different colleagues, pursuing different approaches. In the course of these varied efforts we have drawn some tentative conclusions about general principles that may serve as helpful considerations in designing a research program [1]. In the following essay I will highlight several of these approaches, some of the findings in our and other research groups, and their implications for further study.

2. Heterogeneous catalysis by metal oxides: a hot approach

The "default" mechanism for the first step in an alkane oxidation pathway is homolytic cleavage of a C–H bond, not only because other pathways (acid/base chemistry, electron transfer, etc.) tend to be energetically quite unfavorable for saturated hydrocarbons, but also because oxidation reactions tend to produce reactive radical species. Of course, the homolytic pathway is not all that favorable either. Alkane C–H bonds are relatively strong; furthermore, if we are talking about a reaction catalyzed by a metal oxide, in the dominant Mars–van Krevelen mechanism surface metal-oxo sites, stabilized by strong M–O interactions and hence not particularly reactive either, will be responsible for effecting the C–H cleavage. For adequate reaction rates, then, temperatures on the order of several hundred degrees C or more are needed—a classic hot approach.

Having turned on chemistry by turning up the thermostat, we now need to worry about selectivity. The problem is often stated in general thermodynamic terms: since deep oxidation to carbon dioxide and water is always the thermodynamically favored outcome of an alkane oxidation, we need catalysts that are selective for the first stages of oxidation, stopping at the desired product, and not for subsequent reactions. But it is really more of a fundamental kinetics problem: C–H bond homolysis rates tend to vary inversely with C–H bond strengths, and the products we are after—oxygenates, unsaturated hydrocarbons, etc.—will usually have one or more C–H bonds weaker than those in the starting alkane. (Some typical values are listed in Table 1.) Hence, as long as we are dealing with primarily homolytic mechanisms, it is not at all clear that the problem *can* be solved by catalyst improvement.

A semi-quantitative predictive scheme can be derived [3] using the schematic reaction of Eq. (1), where A is an alkane,

* Tel.: +1 626 395 6520; fax: +1 626 449 4159.
E-mail address: jal@its.caltech.edu (J.A. Labinger).

1381-1169/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2004.03.051

Table 1
Representative C–H bond dissociation energies [2]

Bond type	BDE (kcal/mol)[a]
H–CH_3	105
H–CH_2R	98–101
H–CHR_2	95–99
H–CR_3	93–95
H–CH=CH_2	104–111
H–CH_2CH=CH_2	86
H–C≡CH	132–133
H–CH_2C≡CH	89
H–C_6H_5	111–113
H–$CH_2C_6H_5$	88–90
H–CH_2OH	94–96
H–C(=O)R	86–88
H–CH_2C(–O)R	92–98
H–CH_2CO_2H	97–99

[a] Where ranges are displayed, they represent disagreements between the three compendia used, which may amount to as much as 5 kcal/mol, but the basic relationships between the various types of bond energies are consistent.

B the desired selective oxidation product, and C the result of overoxidation. If B contains weaker C–H bonds than A, we expect that k_2 will be larger than k_1, which will place severe constraints on our ability to make B selectively. To be sure, if such a sequence operates we can *always* make B selectively by staying at very low conversion; but if k_2 is larger than k_1 B will start being consumed faster than it is generated when we reach conversions of any practical relevance. Fig. 1 shows the dependence of the maximum possible yield (i.e., conversion times selectivity) of B on the parameter $R = k_2/k_1$, assuming a simple batch reactor.

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C \quad (1)$$

For example, consider the selective oxidation of methane to methanol. From Table 1, we can see that the C–H bonds in methanol are *substantially* weaker than those in methane, so we can confidently anticipate a large R value. Indeed, R ranges from around 20 for the most reactive, least selective hydrogen-abstracting species such as hydroxyl radical to

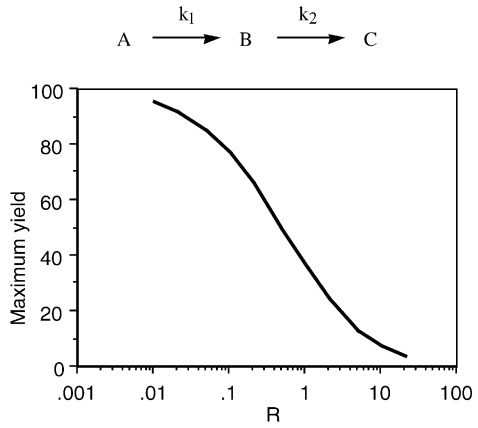


Fig. 1. Maximum yield of B in Eq. (1) as a function of the ratio k_2/k_1.

around 100 or more for "milder" radicals [4]. From Fig. 1, in turn, we would predict that the best yield obtainable for selective oxidation of methane to methanol over a heterogeneous catalyst (or homogeneously in the gas phase, which will also proceed via radical chemistry) should be around 5%. This limit corresponds quite closely to experimental findings [5]; occasional claims of better performance [6] have not stood up to attempted replication.

Similar arguments can be made with respect to the oxidative coupling of methane, an area we were active in around 15–20 years ago [7]. Kinetic modeling of results on one catalyst [7a], coupled with extrapolations and estimates of how much better an "ideal" catalyst might be able to do, indicates a ceiling of around 30% yield [7d], again a prediction that has not been surpassed experimentally. Following the more simple-minded approach of Fig. 1, one might take an R value on the order of 1, as the reactivities of methane and ethane towards highly reactive radicals at high temperature are fairly similar, which likewise predicts a maximum yield around 30%. (As shown in Table 1 the C–H bond strength in ethylene, the most probable next product after ethane, is *higher* than that of methane, so one might expect H atom abstraction to be slower, permitting a higher yield. However, ethylene can undergo radical addition reactions as well, leading eventually to deep oxidation. Experimentally, ethylene fed separately is, in fact, *more* reactive than methane [7a].) A very recent study, employing a much more sophisticated model, leads to almost exactly the same quantitative conclusions [8].

This analysis implies that there are severe *inherent* constraints—i.e., applicable to any catalyst—on the use of high-temperature heterogenous catalysis for selective oxidation of alkanes to species with weaker C–H bonds. Much the same conclusion was reached from an analogous analysis based purely on bond energies (those authors considered C–C as well as C–H bond energies, although it is far from clear that the strong correlation between bond strength and kinetic reactivity would extend across different bond types) [9].

There is also another implication, which at first sight appears rather paradoxical. For the situation described above, assuming that we cannot expect to achieve R values less than 1, our best result would be to get R as close to 1 as possible. But that means we want, in a sense, an *unselective* catalyst. That is, we should use a hydrogen abstractor which is *so* reactive that it does not discriminate much between different C–H bonds, and/or we can run the reaction at as high a temperature as possible, to minimize the effect of bond strength on reaction rate. This strategy, though highly counterintuitive, seems indicated to make the best of a fundamentally unfavorable situation, as we pointed out (others have also [10]) in our earlier analysis of oxidative coupling [7a].

So which targets *do* appear attractive as products of heterogeneously catalyzed selective alkane oxidation? Not alcohols, to be sure; for alkanes higher than methane there is the further difficulty that the bond-strength argument will

always favor oxidation at more substituted C–H positions, whereas the product of terminal oxidation will more commonly be the desired one. One would think not aldehydes either, as the aldehydic C–H bond strength is considerably weaker even than that of methanol (Table 1). However, there *have* been some reports of better yields than one might expect, particularly for methane to formaldehyde. As with methanol, some of the better-looking results with heterogeneous catalysts [11] have not proved reproducible, but in homogeneous gas-phase reactions (with NO_x as a promoter), yields up to 15% have been reported, even though these surely involve radical chemistry [12]. Yields over 10% have also been reported for propane to acrolein [13].

The weaker C–H bond strength *does*, in fact, result in greater reactivity of aldehydes towards most radical hydrogen atom abstractors [4] (a situation which is exploited in the so-called Mukaiyama epoxidation of alkenes [14]), so one would expect a maximum yield of formaldehyde from methane no better than that of methanol. Why can we apparently do considerably better? The answer is not clear; theory might be effectively brought to bear here.

On the other hand, C–H bonds adjacent to carbonyl groups are only slightly, if at all, weakened relative to alkanes, so oxidations such as propane to acetone or ethane to acetic acid ought to be achievable with at least moderately good yield. Best of all would be to have all C–H bonds in the product *stronger* than those for alkanes: olefinic, acetylenic or aromatic C–H bonds only. Oxidative coupling/dehydrogenation of methane all the way to benzene would seem an attractive target, since the non-oxidative variant, over Mo/ZSM-5, is limited by thermodynamics; one might think the H_2 produced could be removed oxidatively under conditions where the product resists overoxidation. Unfortunately in the presence of oxidizing species the catalytic metal carbide sites are destroyed [15]. (Modest increases in conversion beyond equilibrium have been achieved with a hydrogen-permeable membrane reactor [16].)

The prime exemplar is the one commercially practiced selective alkane oxidation, butane to maleic anhydride, over a VPO catalyst. There have been few if any other catalysts that even come close to the performance of VPO, which is itself extremely sensitive to details of catalyst synthesis and morphology; this observation has been interpreted (by some workers in the field) in terms of a specific geometric "fit" between the surface structure and the reactants/intermediates/products [17]. Such a model might be further supported by the fact that VPO is *not* an effective catalyst for other selective oxidations which are "allowed" by the C–H homolysis criterion—ethane (to ethylene and/or acetic acid) and propane (to acrylic acid) [18]. (It should be noted though that *higher* alkanes are oxidized to maleic anhydride over VPO [19].)

If the VPO-butane combination were truly unique, because of this geometric-fit model, bond-strength considerations such as those argued for above would be of only minor relevance at best. However, we have developed a selective oxidation catalyst—based on the $PMo_{11}V$ Keggin ion, exchanged with Nb and reduced with pyridine—that is *substrate-versatile*. We have previously reported that it catalyzes both the butane to maleic and propane to acrylic reactions, with selectivities and yields approaching, and productivities substantially surpassing, the best reported catalysts for each [20]. More recently we have found that it is also highly effective, especially in terms of productivity, for oxidizing ethane to a mixture of ethylene and acetic acid [21]. Some typical comparative performance data is shown in Table 2.

An additional highly suggestive finding is that maleic anhydride is a significant co-product from propane oxidation: a C4 product from a C3 feed. Mechanistic analysis implicates competing acid-catalyzed dimerization of propylene to branched hexenes, which are oxidatively degraded to maleic; there may also be a contribution from dimerization of allyl radicals to 1,5-hexadiene [25]. In any case, the result minimally demonstrates a *mobile* intermediate, implying that the geometric fit argument (even if it has *some* relevance to an explanation of VPO catalysis) is *not* generally applicable to selective alkane oxidation.

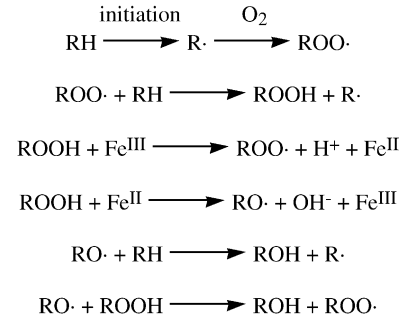
The overall implication of the foregoing discussion is that high-temperature heterogeneously catalyzed (or gas-phase) selective oxidation of alkanes *can* work quite well, but only if we let the chemistry tell us what products we should go after. For desired products with weaker C–H bonds alternative approaches appear more promising. One can of course postulate "fixes" involving reactor design, molecular engineering, etc. For example, a catalyst surface that adsorbs

Table 2
Best performance for selective oxidation of three different alkanes over Keggin ion-derived catalysts and benchmark literature catalysts[a]

Reaction		Keggin-derived catalyst	Benchmark literature results	Reference
C4 to maleic	Best yield (%)	29	~50	[22]
	Best productivity[b]	0.84	~0.07	
C3 to acrylic	Best yield (%)	11	~50	[23]
	Best productivity[b]	0.62	~0.02	
C2 to acetic	Best yield (%)	5	~1	[24]
	Best productivity[b]	0.062	~0.02	

[a] Conditions vary; for Keggin catalysts typically hydrocarbon-rich feed, steam added, 380 °C (see [20,21] for details).
[b] mmol product/min/g catalyst.

alkane more strongly than product; permeable reactor walls that selectively pass product; a hydrophobic active site environment that tends to expel polar product while retaining nonpolar alkane. Neither of the first two appears highly probable, and the third would be difficult to maintain at the high temperatures needed for heterogeneously catalyzed oxidation; but they are not inherently impossible, and perhaps some clever implementation of one or more may be devised. It is more likely, though, that such strategies can be brought to bear for catalytic systems that operate via radical pathways under much milder conditions, as discussed in the following section.



Scheme 1. Key steps in the iron porphyrin-catalyzed autoxidation of isobutane.

3. Biological and biomimetic oxidation: another "hot" approach?

Enzymes that catalyze selective oxidation of one or more alkanes under ambient conditions—most notably the heme-based cytochromes P450 and the non-heme methane monooxygenases (MMO)—are well known. Furthermore, a very large number of metal complexes of varying complexity, ranging from close structural analogs of the enzymatic active sites to fairly simple metal salts, can also effect alkane oxidation with some selectivity, although rarely if ever approaching that of the real enzymes. These latter catalyst systems, often termed "biomimetic", sometimes use molecular oxygen but frequently require more reactive oxidants, such as peroxides, hypochlorite, iodosylbenzene, amine N-oxides, etc. They, too, frequently operate at or near room temperature.

So why do I call this another "hot" approach? Because it appears that the large majority of so-called biomimetic systems, and possibly the biological ones as well, activate alkanes in a manner that bears considerable mechanistic similarity to that of the high-temperature systems of the previous section. That is, homolytic C–H bond cleavage is still involved, but it is achieved by generating a "hot" H-abstracting species (i.e., a metaphorically, as opposed to literally, hot approach), under mild conditions.

This is a rather contentious suggestion to make, in a field that is rather contentious, and a thorough justification (along with the extensive literature review that would be entailed) would be well beyond the scope of this article. I will discuss it only briefly, with emphasis on the potential for a practical approach to selective alkane oxidation, and provide a few recent references and reviews [26] which may serve as starting points for the reader interested in going further.

There are actually (at least) *two* contentious issues here, which are not always clearly distinguished. First, does a given catalyst function by providing an "exotic" site that is unusually reactive towards alkanes, or does it simply act as a means for generating more ordinary reactive radicals? (This probably applies only to the biomimetic class of catalysts, not actual enzymatic systems.) We worked in this area about 10 years ago, collaborating with a group from Sun who had demonstrated that an iron complex of a perhalogenated porphyrin, octabromotetrakis(pentafluorophenyl)porphyrin, functions as an active and selective catalyst for aerobic oxidation of isobutane to *t*-butanol [27]. The original mechanistic proposal was that the active reagent is a ferryl species, Fe=O, related to the presumed active site in cytochromes P450, a class of heme-based oxygenases. This could thus be called a biomimetic oxidation; however, since the synthetic system is able to use *both* atoms of oxygen in O_2 for substrate oxygenation (in contrast to P450, a "monooxygenase" which uses only one of the two), the term "suprabiotic" was offered. However, experimental [28] and modeling [29] studies demonstrated that the reaction here actually proceeds via a free-radical chain autoxidation pathway, where the C–H bond-breaking reagents are ordinary reactive radicals such as *t*-butoxy; the metal complex serves *only* to facilitate generation of those radicals. A simplified mechanism is shown in Scheme 1.

Distinguishing between these alternatives—a metal-based oxidant vs. a radical chain autoxidation pathway—is not always (not often?) straightforward. One example of the potential for complexities was explicated in a paper bearing the evocative title: "A Putative Monooxygenase Mimic Which Functions via *Well-Disguised* (my italics) Free Radical Chemistry" [30]. Similarly, the mechanistic nature of Barton's so-called Gif system and related variants has been the subject of active debate for a number of years, although the preponderance of evidence seems to be settling on free radicals [31]. In many other cases there is good evidence for a metal-centered oxidant.

However, that brings us to the second issue: even if metal-based oxidants are definitely involved, they may also operate as hydrogen atom abstracting agents. Indeed, for many years the consensus mechanism for P450 was the so-called rebound pathway, wherein the active species is believed to be a ferryl (often represented as an Fe(V) oxo complex but perhaps more accurately described as Fe(IV)=O complexed by porphyrin radical cation), generated from an Fe(II)–dioxygen complex by partial reduction and protonation (liberating water). Alternatively, an analogous ferryl can be obtained in model iron porphyrin complexes using oxygen atom-transfer reagents such as iodosylbenzene.

$$RH + (por^{+\cdot})Fe^{IV}{=}O \longrightarrow R\cdot + (por)Fe^{IV}\text{-}OH$$

$$R\cdot + (por)Fe^{IV}\text{-}OH \longrightarrow ROH + (por)Fe^{III}$$

Scheme 2. Rebound mechanism for alkane oxidation by P450 (por: porphyrin ligand).

The oxygen center of the ferryl pulls off an H atom from RH to produce a short-lived radical, which rapidly reacts with the Fe–OH group thus formed to give product ROH (Scheme 2). This mechanism appeared consistent with various observations, including selectivity for substituted positions (terminal positions are unreactive; methane is not oxidized at all by P450s), large kinetic isotope effects, and stereochemical scrambling [32].

Methane monooxygenases (MMO), in contrast, are non-heme iron enzymes that *do* oxidize methane, and show substantial reactivity for terminal alkane positions in general. (At least, the foregoing is true for the better-studied soluble forms of MMO; there are also membrane-bound forms which appear to be based on copper centers and which exhibit strong-to-exclusive *non*-terminal regioselectivity [33].) An obvious and crucial question: does the difference in regioselectivity point to a fundamentally different mechanism? Or are the mechanisms basically similar, with regioselectivity determined by geometric constraints imposed by the protein chain environment around the active site?

For a number of years, researchers in the field wished that the MMO mechanism could be brought to a level of understanding comparable to that for P450. As the saying goes, be careful what you wish for: that state has to a large extent been reached, but it is in large part a consequence of increased confusion over the P450 mechanism! In particular, a number of findings seem to be incompatible with the standard rebound model, notably the behavior of certain "radical clock" substrates which would require rebound to occur at an almost impossibly fast rate (on the order of vibrational lifetimes) to accommodate the observed absence of rearrangement. There is no current universally accepted picture, but the trend is to invoke multiple oxidizing species, multiple spin states, and multiple mechanisms (perhaps involving cationic as well as radical intermediates) to account for the various observations [34]; this may well apply to model systems as well [35,36].

For MMO much of the behavior seems to be fairly similar, in terms of rearrangements, isotope effects, etc. although there are still a large number of hard-to-explain details [37]. Comparative computational studies suggest that the C–H activation mechanism is basically the same in the two systems [38]. The process seems best described as a hydrogen atom abstraction, although the subsequent intermediate (if indeed there is any species that can be comfortably described as a discrete intermediate) does not behave like a true free radical.

If this is a correct description, it suggests that many of the difficulties we encountered in high-temperature heterogeneous catalysis—inherent propensity for overoxidation (generally) wrong preferred regioselectivity—should apply to this approach as well. Nonetheless, the enzymatic systems solve these problems (obviously). Presumably they do so by the tricks suggested at the end of the preceding section: "engineering" the active site so as to expel products before they are overoxidized, restricting access to alkane positions that are mechanistically disfavored, etc. But our ability to use the actual biological catalysts for practical processes (especially large-scale ones) is probably quite limited; and it is far from clear how far we will be able to extend molecular engineering in purely synthetic, biomimetic catalysts. Surely the selectivity for methane achieved by MMO is the result of something *much* more elaborate than a narrow, restrictive entry channel. A number of MMO "mimics", some modeling the enzyme active site structure (known crystallographically) quite closely, will reproduce some features of MMO activity, including hydroxylation of higher alkanes; but none has yet been found that oxidizes methane at all, let alone preferentially.

Hopefully, as detailed understanding of the enzymatic alkane oxidations improves, we will start to discover ways to build some of Nature's "tricks" into our model systems. Alternatively, we may get Nature to show us the way herself, using directed evolution and related protein engineering methodology [39]; by evolving improved oxygenating enzymes and comparing them to wild-type analogs we should be able to sort out some of the key structural features, and *perhaps* to incorporate them in synthetic analogs. But the complexity of biological systems must not be underestimated; it is quite possible that this approach will not pay off, in any practical sense, until well into the future.

4. Organometallic activation of C–H bonds: a cold approach

The activation of alkanes by organo-transition metal complexes can be achieved under remarkably mild conditions, in a manner mechanistically quite different from homolytic hydrogen atom abstraction. In principle, then, this truly "cold" approach has the potential for evading the selectivity constraints that characterized most of the examples in the two previous sections; in practice, however, major difficulties are encountered when trying to exploit that potential for practical processes [40].

Up to about 20 years ago, it had generally been thought that trying to use transition metals to activate alkanes would face the same problem—general inertness—that hinders other approaches. There were a number of examples of C–H bond activation in *unsaturated* hydrocarbons, such as arenes; but these seemed to pose less of a problem, as there were well-established bonding models whereby an initial interaction between hydrocarbon and metal center could be established. Examples of intramolecular activation of saturated groups, as for example, H–D exchange in an alkyl group of a phosphine ligand, were also known, but here

the entropic assistance of the intramolecular reaction was thought to be crucial. A (much smaller) number of catalytic reactions of alkanes had been reported, but were poorly if at all understood [41].

A key development occurred in 1982, when two groups reported reactions of the stoichiometry shown in Eq. (2) [42,43]. One *might* have still argued, especially for the case, where Cp = C_5Me_5 and L = PMe_3, that this worked by virtue of the extreme electron-richness of the unsaturated metal center generated by photoelimination of H_2—in other words, that this is another "hot" reagent—but a very large number of well-defined examples followed in short order [44], establishing that alkane activation by transition metal centers is really rather facile; no extreme reactivity is required.

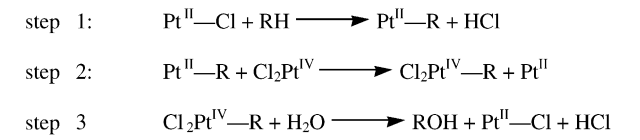
$$\mathrm{Cp(L)IrH_2 + RH \xrightarrow{h\nu} Cp(L)Ir(R)(H) + H_2}$$
$$(\mathrm{Cp = C_5H_5, L = CO; Cp = C_5Me_5; L = PMe_3}) \quad (2)$$

It seems clear from the reactivity (some reactions of this type can be observed well below room temperature) and stoichiometry of these and related transformations that C–H homolysis is not involved, and that is further supported by trends in regioselectivity, as primary positions are generally the favored site of attack. Alkane oxidation products, then, might *not* necessarily be more reactive than alkanes (depending upon what the C–H activation mechanism actually is), so that more selective oxidations could be achievable. However, another difficulty immediately arises: organometallic complexes such as those used in Eq. (2), and the vast majority of C–H activating complexes as well, are highly sensitive to O_2 or other oxidants, and would be instantly destroyed under catalytic oxidizing conditions.

Our attention was thus drawn to some older work—indeed, the earliest reports of alkane oxidation mediated by discrete metal complexes. In the early 1970s a Russian group led by Shilov, following up on earlier observations of alkane H–D exchange catalyzed by platinum complexes, reported the chemistry shown in Eq. (3). Here a simple Pt(II) complex, air- and water-stable, effects C–H activation that leads to the "catalytic" oxidation of alkanes to alcohols [45]. The scare quotes here are to emphasize that the conversion is catalytic in Pt(II) but stoichiometric in Pt(IV), the net oxidant, and hence clearly not practical as thus constituted. But *if* Pt(IV) could be replaced by a much cheaper oxidant (ideally O_2), and *if* the nature of C–H activation does indeed lead to the selectivity patterns desired, this reaction could be the basis of a very promising approach. To answer both of those "ifs" detailed mechanistic understanding is required.

$$\mathrm{RH + H_2O + PtCl_6^{2-} \xrightarrow[PtCl_4^{2-}]{H_2O,\ 120\,^\circ C} ROH + PtCl_4^{2-} + 2HCl} \quad (3)$$

Extensive mechanistic studies by our group and others have established the three-step mechanism shown in Scheme 3 [45]. The nature of steps 2 and 3 are the easier ones to investigate: they involve electron transfer (as opposed to alkyl group transfer) and nucleophilic attack by water on the C–Pt bond, respectively [46]. The first of those findings implies that the oxidant need not be Pt(IV), and indeed there has been some success with alternate oxidants, most notably with the Wacker-like reoxidation system O_2/Cu [47], although only modest activity and catalyst lifetime has yet been achieved.

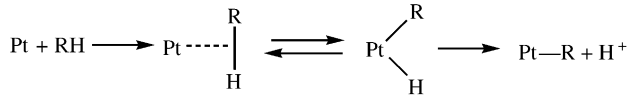


Scheme 3. Mechanism of Shilov oxidation (non-participating ligands omitted).

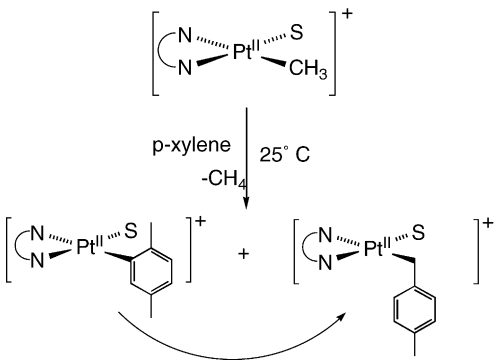
The first step is much more difficult to study, because (among other reasons) the intermediate Pt(II) alkyl is not stable. However, a variety of experiments using model systems, isotopic labeling, and kinetics all implicate a mechanism whereby alkane initially interacts with the Pt(II) center in the form of a "sigma complex"; that is, the alkane acts as a ligand by using a C–H sigma bonding pair to donate to a vacant Pt orbital. The sigma complex is in facile equilibrium with the C–H bond cleavage product, and deprotonation leads to the Pt(II)–R intermediate, as shown in Scheme 4 [48].

Such alkane complexes have been implicated in a very large number of systems [49]. (Most often the experimental evidence involves transient spectroscopy or isotopic labeling experiments; there is one example of a complex sufficiently stable to observe directly by NMR [50], and a couple of crystal structures, although these involve additional non-covalent stabilizing interactions as well [51].) It seems certain that they will play a central role in selective alkane oxidation by transition metal complexes, both by providing a low-energy pathway for the C–H bond activation and, presumably, in controlling selectivity patterns quite different from those encountered in radical chemistry.

It should be noted that the origin of regioselectivity is not always clearcut. Reactions of the sort shown in Eq. (2) exhibit strong preference for terminal alkyl products, and initially this *appeared* to be a kinetic rather than thermodynamic effect, since it was believed that an initially formed product M(H)(R) could only rearrange to an isomer via complete dissociation and readdition of RH, a process that can be definitively ruled out in many cases [52]. This would suggest that observed selectivities are governed by preferences



Scheme 4. Detailed mechanism of first step (C–H activation) of Shilov oxidation.



Scheme 5. Observed transformations in reaction of cationic Pt(II) complex with *p*-xylene.

in the initial site of attack—the sigma complex—with terminal positions presumably favored for steric reasons. But soon it was recognized that sigma complexes can be sufficiently stable to permit isomerization *without* dissociation. M(H)(R) undergoes "reductive elimination in place" to form the sigma complex M(RH) which can rearrange to another sigma complex, with a different C–H bond coordinated, and then re-add the new C–H bond, all without RH ever leaving the coordination sphere [53]. Hence the selectivities actually reflect thermodynamic preferences for metal–alkyl binding (long known to prefer terminal positions in the vast majority of cases). In any given case an observed selectivity might be the consequence of almost any combination of kinetic and thermodynamic factors, depending on relative rates and equilibria of initial reactions and subsequent rearrangements. Detailed analyses of the latter have been worked out for a couple of systems [54].

Ambiguities can likewise arise in selectivities for different types of C–H bonds, such as alkane vs. arene. The latter is almost always favored, kinetically as well as thermodynamically. Kinetic preferences are usually ascribed to the ability of arenes to interact with the metal via π electrons—the same reasoning that had been offered to explain why arene activation had been demonstrated long before alkane activation. It is true that π-benzene complexes have been observed as intermediates in benzene C–H activation reactions, both spectroscopically [55] and crystallographically [56]; but the geometry would not seem to particularly favor C–H cleavage in any way, and it is perhaps more likely that the π-arene complex does not lie on the direct pathway to C–H bond cleavage, but instead must first rearrange to a sigma complex. A particularly complex situation appeared in one of our studies on hydrocarbons which present *both* types of sites, such as *p*-xylene: the reaction shows kinetic preference for the aryl position and (unusual) thermodynamic preference for the benzylic position (Scheme 5). Evidence suggests that the conversion of the kinetic to thermodynamic product is the result of a secondary reaction, not a simple rearrangement; and the benzylic product may be thermodynamically preferred because of an η^3-structure, a situation limited to benzylic species [57].

In a catalytic reaction, then, overall product selectivity will depend on a number of factors: relative rates of activation of different C–H positions compared not only to each other but (if reversible) to rates of rearrangements and to rates of subsequent product-forming steps. For oxidations in particular, we know relatively little about the reactivities of C–H bonds in alkanes compared to those in oxygenates, but the fact that some selective oxidations have been achieved suggests that they are (at worst) not too unfavorable, and that seems reasonable in principle. For example, one might expect a C–H bond on an electronegatively substituted carbon center to be a poorer donor than one on a simple alkane, which could lead to the desired situation of an alkane being *more* reactive than its oxidation products.

A dramatic illustration of that potential is provided by the oxidation of methane to methyl bisulfate by sulfuric acid, catalyzed by a Pt(II) complex, as shown in Eq. (4) [58]. The mechanism for this reaction is probably closely related to that of the Shilov system (Scheme 3), with sulfuric acid playing the role of oxidant in step 2 and nucleophile in step 3. Most remarkably, the product (a methanol derivative, which can be converted to methanol by hydrolysis) can be obtained in yields around 70%; compare that to the ceiling of 5% predicted for methane to methanol in a radical-based process. According to Fig. 1, and taking into account the low solubility of methane, the rate constant for the reaction of the Pt center with a C–H bond of methane must be around 100 times larger than for a C–H bond of the product, methyl bisulfate, to account for the high yield.

$$CH_4 + 2H_2SO_4 \xrightarrow[180\,^\circ C]{(L_2)PtCl_2} CH_3OSO_3H + SO_2 + 2H_2O \quad (L_2 = \text{bipyrimidine}) \qquad (4)$$

While this system is itself not economically practical, owing in large part to the large quantities of sulfuric acid that would have to be handled and recycled, it validates this approach as a means of achieving highly selective alkane oxidation. Furthermore, it offers greater potential for product-versatility: we may not be so restricted to particular classes of target products as with the high-temperature routes. Certainly there are still formidable obstacles to be overcome; as with the biological/biomimetic approach, much more work needs to be done before we can even assess the likelihood of major accomplishments with any confidence. But this "cold" organometallic approach offers an alternative to the "hot" approaches that clearly involves quite different chemistry, and thereby, perhaps, more promise.

Acknowledgements

I am indebted to all the coworkers whose names may be found in the various references to our work here, particularly my colleagues John Bercaw, Mark Davis and Harry Gray. I am also grateful to Enrique Iglesia for helpful discussions.

References

[1] They can also be very useful as *ex post facto* rationalizations, when needed.

[2] (a) D.F. McMillen, D.M. Golden, Ann. Rev. Phys. Chem. 33 (1982) 493;
(b) J. Fossey, D. Lefort, J. Sorba, Free Radicals in Organic Chemistry, Wiley, New York, 1995, p. 33;
(c) D.R. Lide (Ed.), Handbook of Chemistry and Physics, 80th ed., CRC Press, Boca Raton, 1999, p **9**-64.

[3] J.A. Labinger, J.E. Bercaw, G.A. Luinstra, D.K. Lyon, A.M. Herring, in: R.F. Howe, E. Curry-Hyde (Eds.), Natural Gas Conversion II: Proceedings of the Third International Gas Conversion Symposium, Sydney, 4–9 July 1993, Elsevier, Amsterdam, 1994, p. 515.

[4] See for example, J.K. Kochi (Ed.), Free Radicals, Wiley, New York, 1973, especially Chapters 1, 2, 7, and references cited therein.

[5] E.E. Wolf (Ed.), Methane Conversion by Oxidative Processes: Fundamental and Engineering Aspects, Van Nostrand Reinhold, New York, 1992.

[6] For example, H.D. Gesser, N.R. Hunter, L.A. Morton, US Patent 4,618,732 (1986).

[7] (a) J.A. Labinger, K.C. Ott, J. Phys. Chem. 91 (1987) 2682;
(b) J.A. Labinger, K.C. Ott, S. Mehta, H.K. Rockstad, S. Zoumalan, J. Chem. Soc. Chem. Commun. (1987) 543;
(c) J.A. Labinger, S. Mehta, K.C. Ott, H.K. Rockstad, S. Zoumalan, in: J.W. Ward (Ed.), Proceedings of the 10th North American Catalysis Society Meeting on Catalysis 1987, Elsevier, Amsterdam, 1988, p. 513;
(d) J.A. Labinger, Catal. Lett. 1 (1988) 371;
(e) J.A. Labinger, K.C. Ott, Catal. Lett. 4 (1990) 245.

[8] Y.S. Su, J.Y. Ying, W.H. Green Jr., J. Catal. 218 (2003) 321.

[9] F.E. Cassidy, B.K. Hodnett, CATTECH 2 (1998) 173.

[10] E. Iglesia, personal communication.

[11] (a) For example, R.-S. Liu, M. Iwamoto, J.H. Lunsford, J. Chem. Soc. Chem. Commun. (1982) 78;
(b) T. Sugino, A. Kido, N. Azuma, A. Ueno, Y. Udagawa, J. Catal. 190 (2000) 118.

[12] (a) J.A. Barbero, M.C. Alvarez, M.A. Bañares, M.A. Peña, J.L.G. Fierro, Chem. Commun. (2002) 1184;
(b) A. Sen, M. Lin, in: J.J. Spivey, E. Iglesia, T.H. Fleisch (Eds.), Natural Gas Conversion VI, Studies in Surface Science and Catalysis, vol. 136, Elsevier, Amsterdam, 2001, p. 227;
(c) K. Otsuka, R. Takahashi, K. Amakawa, I. Yamanaka, Catal. Today 45 (1998) 23.

[13] M.Yu. Sinev, O.V. Udalova, Y.P. Tulenin, L.Ya. Margolis, V.P. Vislovskii, R.X. Valenzuela, V. Cortés Corberán, Catal. Lett. 69 (2000) 203.

[14] T. Mukaiyama, T. Yagada, Bull. Chem. Soc. Jpn. 68 (1995) 17.

[15] Z. Liu, M.A. Nutt, E. Iglesia, Catal. Lett. 81 (2002) 271.

[16] Z. Liu, L. Li, E. Iglesia, Catal. Lett. 82 (2002) 175.

[17] (a) See for example, J. Haber, in: E.G. Derouane, J. Haber, F. Lemos, F. Ramoa Ribeiro, M. Guisnet (Eds.), Catalytic Activation and Functionalisation of Light Alkanes: Advances and Challenges, Kluwer Academic Publishers, Dordrecht, 1998, p. 157;
(b) K.C. Waugh, Y.-H. Taufiq-Yap, Catal. Today 81 (2003) 215, and references cited therein.

[18] F. Cavani, G. Centi, A. Riva, F. Trifiro, Catal. Today 1 (1987) 17.

[19] (a) G. Centi, J. Lopez Nieto, D. Pinelli, F. Trifiro, Ind. Eng. Chem. Res. 28 (1989) 400;
(b) F. Cavani, A. Colombo, F. Giuntoli, E. Gobbi, F. Trifiro, P. Vazquez, Catal. Today 32 (1996) 125.

[20] (a) M.E. Davis, C.J. Dillon, J.H. Holles, J.A. Labinger, Angew. Chem. Int. Ed. Engl. 41 (2002) 858;
(b) J.H. Holles, C.J. Dillon, J.A. Labinger, M.E. Davis, J. Catal. 218 (2003) 42;
(c) C.J. Dillon, J.H. Holles, R.J. Davis, J.A. Labinger, M.E. Davis, J. Catal. 218 (2003) 54.

[21] A.P. Wight, C.J. Dillon, J.H. Holles, J.A. Labinger, M.E. Davis, Proceedings of the American Institute of Chemical Engineers Annual Conference, San Francisco, CA, November 2003, Paper 146d.

[22] M.J. Ledoux, C. Crouzet, C. Pham-Huu, V. Turines, K. Koutakis, P.L. Mills, J.J. Lerou, J. Catal. 203 (2001) 405.

[23] T. Ushikubo, H. Nakamura, Y. Koyasu, S. Wajiki, US Patent 5,380,933, Mitsubishi Kasei (1995).

[24] E.M. Thorsteinson, T.P. Wilson, F.G. Young, P.H. Kasai, J. Catal. 52 (1978) 116.

[25] C.J. Dillon, J.H. Holles, M.E. Davis, J.A. Labinger, Catal. Today 81 (2003) 189.

[26] A.A. Fokin, P.R. Schreiner, Chem. Rev. 102 (2002) 1551.

[27] (a) P.E. Ellis, J.E. Lyons, Catal. Lett. 3 (1989) 389;
(b) P.E. Ellis, J.E. Lyons, Coord. Chem. Rev. 105 (1990) 181;
(c) J.E. Lyons, P.E. Ellis, Catal. Lett. 8 (1991) 45.

[28] M.W. Grinstaff, M.G. Hill, J.A. Labinger, H.B. Gray, Science 264 (1994) 1311.

[29] J.A. Labinger, Catal. Lett. 26 (1994) 95.

[30] P.A. MacGaul, K.U. Ingold, D.D.M. Waymer, L. Que, J. Am. Chem. Soc. 119 (1997) 10594.

[31] S. Kiani, A. Tapper, R.J. Staples, P. Stavropoulos, J. Am. Chem. Soc. 122 (2000) 7503, and references cited therein.

[32] M. Sono, M.P. Roach, E.D. Coulter, J.H. Dawson, Chem. Rev. 96 (1996) 2841, and references cited therein.

[33] S.J. Elliott, M. Zhu, L. Tso, H.-H.T. Nguyen, J.H.-K. Yip, S.I. Chan, J. Am. Chem. Soc. 119 (1997) 9949.

[34] M. Newcomb, P.F. Hollenberg, M.J. Coon, Arch. Biochem. Biophys. 409 (2003) 72, and references cited therein.

[35] W. Nam, M.H. Lee, S.K. Moon, C. Kim, J. Am. Chem. Soc. 122 (2000) 10805.

[36] J.P. Collman, A.S. Chien, T.A. Eberspacher, J.I. Brauman, J. Am. Chem. Soc. 122 (2000) 11098.

[37] M.-H. Baik, M. Newcomb, R.A. Friesner, S.J. Lippard, Chem. Rev. 103 (2003) 2385, and references cited therein.

[38] V. Guallar, B.F. Gherman, S.J. Lippard, R.A. Friesner, Curr. Opin. Chem. Biol. 6 (2002) 236.

[39] P.C. Cirino, F.H. Arnold, Curr. Opin. Chem. Biol. 6 (2002) 130, and references cited therein.

[40] J.A. Labinger, J.E. Bercaw, Nature 417 (2002) 507.

[41] A.E. Shilov, A.A. Shteinman, Coord. Chem. Rev. 24 (1977) 97.

[42] A.H. Janowicz, R.G. Bergman, J. Am. Chem. Soc. 104 (1982) 352.

[43] J.K. Hoyano, W.A.G. Graham, J. Am. Chem. Soc. 104 (1982) 3723.

[44] A.E. Shilov, G.B. Shul'pin, Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes, Kluwer Academic Publishers, Dordrecht, 2000, and references cited therein.

[45] A.E. Shilov, G.B. Shul'pin, Chem. Rev. 97 (1997) 2879, and references cited therein.

[46] G.A. Luinstra, L. Wang, S.S. Stahl, J.A. Labinger, J.E. Bercaw, J. Organometal. Chem. 504 (1995) 75, and references cited therein.

[47] M. Lin, C. Shen, E.A. Garcia-Zayas, A. Sen, J. Am. Chem. Soc. 123 (2001) 1000.

[48] (a) S.S. Stahl, J.E. Labinger, J.A. Bercaw, J. Am. Chem. Soc. 118 (1996) 5961;
(b) H.A. Zhong, J.A. Labinger, J.E. Bercaw, J. Am. Chem. Soc. 124 (2002) 1378.

[49] C. Hall, R.N. Perutz, Chem. Rev. 96 (1996) 3125.

[50] S. Geftakis, G.E. Ball, J. Am. Chem. Soc. 120 (1998) 9953.

[51] (a) D.R. Evans, T. Drovetskaya, R. Bau, C.A. Reed, P.D.W. Boyd, J. Am. Chem. Soc. 119 (1997) 3633;
(b) I. Castro-Rodriguez, H. Nakai, P. Gantzel, L.N. Zakharov, A.L. Rheingold, K. Meyer, J. Am. Chem. Soc. 125 (2003) 15734.

[52] See for example, W.D. Jones, F.J. Feher, J. Am. Chem. Soc. 106 (1984) 1650.

[53] R.A. Periana, R.G. Bergman, J. Am. Chem. Soc. 108 (1986) 7332.

[54] (a) T.O. Northcutt, D.D. Wick, A.J. Vetter, W.D. Jones, J. Am. Chem. Soc. 123 (2001) 7257;
(b) T.C. Flood, K.E. Janak, M. Iimura, H. Zhen, J. Am. Chem. Soc. 122 (2000) 6783.
[55] L. Johansson, M. Tilset, J.A. Labinger, J.E. Bercaw, J. Am. Chem. Soc. 122 (2000) 10846.
[56] S. Reinartz, P.S. White, M. Brookhart, J.L. Templeton, J. Am. Chem. Soc. 123 (2001) 12724.
[57] A.F. Heyduk, J.A. Labinger, J.E. Bercaw, submitted for publication.
[58] R.A. Periana, D.J. Taube, S. Gamble, H. Taube, T. Satoh, H. Fujii, Science 280 (1998) 560.