

ORGANOMETALLIC CHEMISTRY

C-H activation

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The stability of the chemical bonds in saturated hydrocarbons makes them generally unreactive. But the invention of processes in which carbon-hydrogen (C-H) bonds in hydrocarbons can be activated is allowing chemists to exploit organic compounds in previously unimaginable ways.

Why is C-H activation such big news?

These reactions could revolutionize the chemical industry. Natural gas, for example, is best known as a fuel. But it is also a vast, low-cost feedstock of hydrocarbons that remains untapped as a raw material, simply because there has been no easy way of turning it into synthetically useful compounds. This could be about to change. Methane — CH_4 , the main constituent of natural gas — can now be converted directly into derivatives of methanol (CH_3OH) in a high-yielding C-H activation reaction that is catalysed by metal salts in solution. Methanol is the starting point for many industrial processes, and is ultimately incorporated into such products as plastics and paints. C-H activation also allows chemical groups to be placed directly in a molecule where none existed before, a process that previously often needed several steps. This is especially useful for shortening multi-step syntheses, which are commonly used in drug discovery.

What stimulated chemists to work on C-H activation?

C-H bonds are ubiquitous in organic molecules, yet many of these could not be exploited for chemical reactions. A few methods were available, but these were unselective — they yielded a complicated mixture of products. So the uncharted territory of C-H bond reactivity was an irresistible area for chemists to explore. More pragmatically, it was, perhaps, the realization that hydrocarbon feedstocks are inefficiently used. Organic molecules, based on carbon chains, are the basis of most of the non-metallic materials found in everyday life. Plastics, for example, have replaced metals and ceramics in many applications. These organic materials are made by chemical synthesis from the hydrocarbons found in petroleum. But there's a problem: only about half of the hydrocarbons are reactive enough to take part in traditional chemical reactions. C-H activation gets around this by stimulating inert hydrocarbons to react with other molecules.

Why are only half of the hydrocarbon feedstocks chemically reactive?

The answer lies in the stability of their chemical bonds. Hydrocarbons are simple molecules that contain only carbon-carbon (C-C) and carbon-hydrogen (C-H) bonds (Fig. 1). There are two general classes: saturated hydrocarbons (alkanes), which contain only single bonds, and unsaturated hydrocarbons (arenes, alkenes and alkynes), which also contain some C-C multiple bonds. The single bonds in hydrocarbons are very stable, which is why alkanes are quite inert, although they can be slowly oxidized, unselectively, in air. But the C-C multiple bonds in unsaturated hydrocarbons are far less stable and so are more prone to chemical attack than are C-C or C-H single bonds.

How are hydrocarbons converted into more useful compounds?

Many reagents have been developed that introduce synthetically useful chemical groups into unsaturated hydrocarbons. At one time, these reagents were primarily other organic compounds, or were based on elements from the main groups of the periodic table. But some of the best modern reagents are based on transition metals such as iron, osmium, palladium, rhodium and ruthenium. This has created a research boom in organometallic chemistry — the interdisciplinary area that lies between organic and inorganic chemistry.

So what's the problem?

There are two. First, if a chemist wants to perform a reaction with an alkane, he or she is forced to 'activate' single bonds (either C-C or C-H) in the molecule, so that they become prone to chemical attack. Second, there is very little difference in reactivity between the various C-H bonds in alkanes, so targeting a specific C-H bond is difficult. Currently, very few reagents can activate specific C-H bonds in alkanes under mild reaction conditions.

What exactly is meant by 'activation'?

Most generally, this means treating a C-H bond in some way that allows a reagent to react

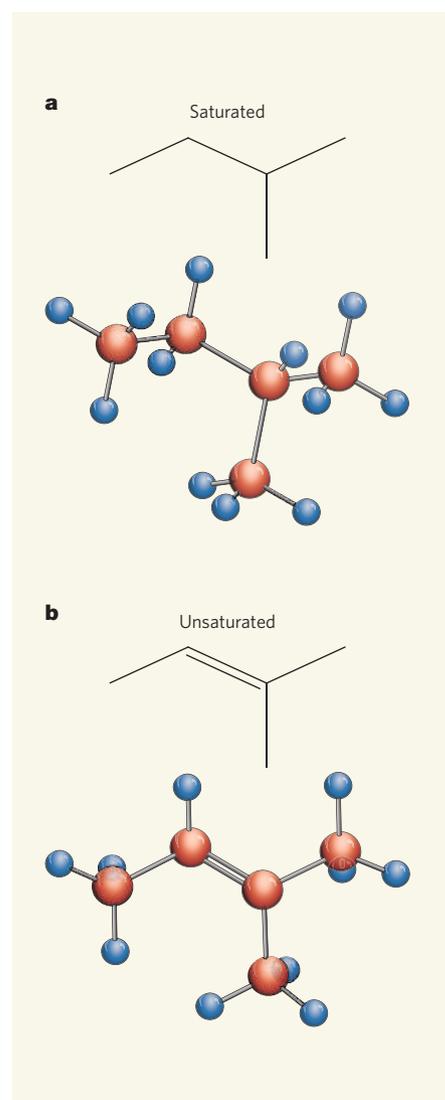


Figure 1 | Saturation in hydrocarbons. **a**, Saturated hydrocarbons are usually represented as shown in the top structure. The ball-and-stick model underneath shows that they consist of carbon (red) and hydrogen atoms (blue) connected by single bonds. **b**, Unsaturated hydrocarbons also contain some double bonds, which are more reactive than single bonds and make unsaturated hydrocarbons more reactive than saturated ones.

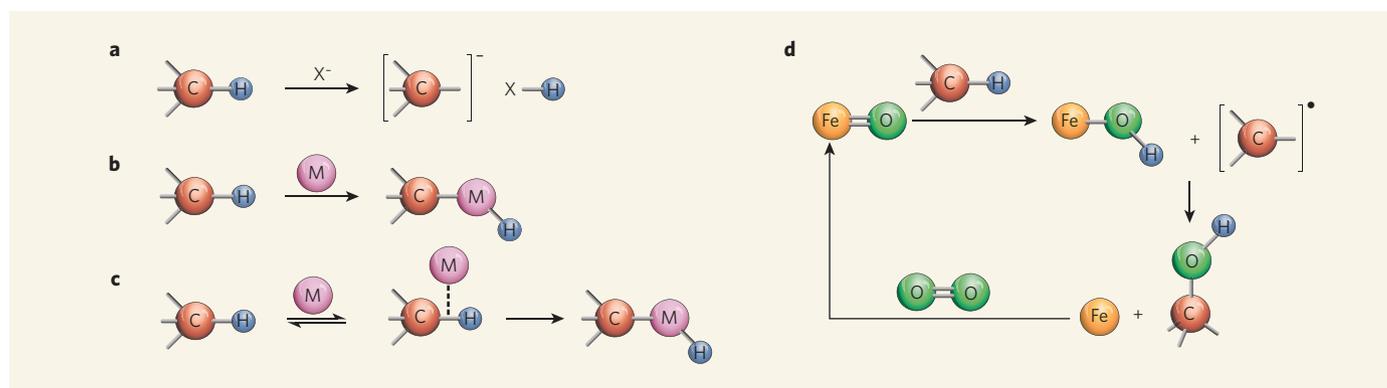


Figure 2 | Mechanisms for C-H activation reactions. **a**, Classical methods for C-H activation reactions simply removed the hydrogen atom, using either a base (X^- , as shown here), a free radical or an electrophile (reactions for the last two reagent types are not shown for simplicity). **b**, In oxidative addition reactions, a metal atom (M) inserts itself between the atoms of the C-H bond. **c**, The latest data suggest that oxidative additions proceed in two steps. A metal binds weakly to the C-H bond in an equilibrium process, before inserting

itself between the atoms of the bond. **d**, The active sites of certain enzymes contain iron complexes in which iron (Fe) is bound to oxygen with a double bond. These might react with C-H bonds to yield a carbon radical (indicated by the dot) and an intermediate iron complex containing a hydroxyl group (OH). If the hydroxyl group transfers to the carbon atoms, the remaining iron complex could then be oxidized back to its original form, ready to repeat the cycle with another C-H bond. Atoms are not drawn to scale.

rapidly with the carbon atom. A second reaction then yields a stable product in which the C-H bond is replaced by a new bond, C-X, where X is often a nitrogen, oxygen or carbon atom in another molecule. The classical methods for this simply involved removing the hydrogen, possibly along with one or two of the bonding electrons (Fig. 2a). But these methods usually required a chemical group to be adjacent to the targeted C-H bond — saturated hydrocarbons, by definition, possess no such chemical groups. Alternatively, 'brute-force' reagents were required, such as strong acids or bases, or reactive free radicals; this compromised the selectivity of the reactions and prevented them from being performed under mild conditions.

What was the solution to these problems?

The solution was a new kind of reaction, reported in the late 1960s (Box 1). In these so-called oxidative addition reactions, a metal from a soluble metal salt or complex seems to insert itself between the atoms of a C-H bond, yielding an unstable product that contains a carbon-metal bond and a metal-hydrogen bond (Fig. 2b). The oxidation state of the metal increases during the transformation, hence the name oxidative addition. The latest evidence suggests that oxidative addition is not a simple one-step process. Instead, it seems to proceed through an intermediate in which the C-H bond is weakly bound to the metal centre, but where the C-H bond is not yet broken (Fig. 2c). The idea that a simple C-H bond, which does not have electrons that are readily available for binding to metals, could behave in this way is unprecedented. An understanding of such mechanistic details is crucial for developing the next generation of C-H activation reactions.

Are there any other methods for activating C-H bonds?

Another possible route uses solid metallic materials — known as heterogeneous catalysts

— that can also react with C-H bonds. These reactions are more complicated than simple oxidative addition reactions (which take place in solution) and the mechanisms are more difficult to identify by spectroscopic techniques because the catalysts don't dissolve. This method of C-H activation has been studied extensively by physical chemists and chemical engineers, and constitutes a separate subject in its own right.

When did C-H activation really take off?

The field took off during the 1980s, when there was a dramatic increase in the number of metal salts and complexes that were found to initiate C-H activation by oxidative addition. But the drawback was that most of these transformations required equal amounts, in moles, of the hydrocarbon and the metal, and both partners were consumed during the reaction. This is not acceptable for large-scale chemistry, as the metals involved are generally more expensive than the products.

What is being done to improve the chemistry?

There has been an explosion of interest in the use of catalytic reactions for bringing about oxidative addition for C-H activation. In these catalytic processes, the oxidative addition product is a transient intermediate that immediately reacts with other reagents to introduce a new atom. The catalytic metal is released so that it can attack another molecule of hydrocarbon. Because the metal is not consumed, such reactions often need only tiny amounts of catalyst. An excellent example is the recent discovery that rhodium catalysts directly convert the C-H bonds at the ends of alkane chains into carbon-boron bonds; the products of such reactions are very useful for synthetic organic chemistry. Another example is the discovery that methane can be converted into methanol derivatives with unusually high

yields using platinum complexes in strong acid solution. Catalytic reactions are especially important in nature, where enzymes (many of which bear metals at their active sites) mediate a wide range of biological transformations.

Are there any enzymatic C-H activation reactions?

Yes, some very important ones. Cytochrome P450 enzymes typically catalyse the conversion of C-H bonds to C-O bonds in organic compounds. In humans, these enzymes are involved in making cholesterol, steroids and other lipids; they also metabolize drugs, converting them to highly oxidized compounds that can be excreted by the body. The active sites of these enzymes contain iron atoms that play a crucial role in the C-H activation process. Another striking example of a C-H activating enzyme is methane monooxygenase, which was recently discovered in a class of bacterium that lives at the interface of aerobic and anaerobic environments. This enzyme converts methane to methanol, although it can also oxidize several other organic compounds.

Is there anything we can learn from these enzymes?

They have already shown us a completely different approach to C-H activation. The enzymes mentioned above have iron (Fe) ions at their active sites. Current evidence suggests that these iron centres react with oxygen to make a highly reactive iron-oxygen double bond, Fe=O (Fig. 2d). The critical activation step involves the addition of the atoms in a C-H bond to the Fe=O intermediate, perhaps yielding a carbon radical and a complex bearing an iron-hydroxy (OH) group, before the formation of a C-OH bond. However, the details of this process are still a source of controversy.

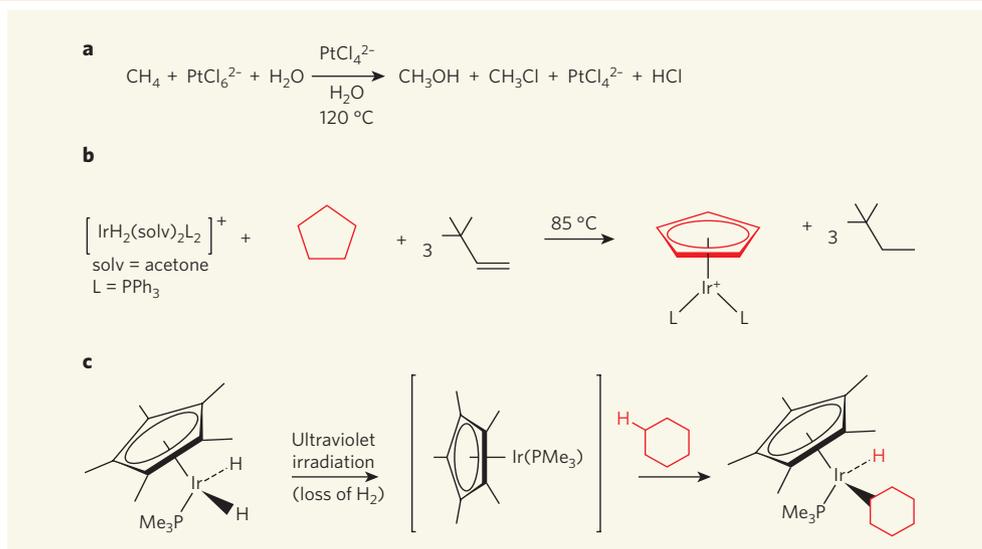
Could a synthetic version of the enzyme reaction be produced?

It is difficult to develop simple artificial

Box 1 | The birth of C–H activation

The origins of the field lie in the 1960s and 1970s, when C–H activation was spotted in saturated molecules in intramolecular reactions (where the metal and the C–H bond are in the same molecule). The first activation reactions of C–H bonds in aromatic molecules were also observed in this period. This led the pioneering organometallic chemist Jack Halpern to comment in 1968 that “the development of successful approaches to the activation of carbon–hydrogen bonds, particularly in saturated hydrocarbons, remains to be achieved and presently constitutes one of the most important and challenging problems in this whole field”.

At about the same time, several groups observed that hydrogen atoms in saturated hydrocarbons (alkanes) could be replaced with isotopic deuterium atoms using metal complexes. Even more intriguing were studies showing that alkane hydrogens could be directly replaced with other atoms or chemical groups using platinum (Pt) salt complexes (**a** in the figure). Although these reactions were rather inefficient,



they converted simple alkanes into more complex molecules that contained new carbon–chlorine or carbon–oxygen bonds. The mechanisms underlying these processes are still not completely understood today.

In the late 1970s, it was found that certain organometallic compounds (made with the metals rhenium and iridium, Ir) could be used to remove hydrogen from

alkanes, so yielding unsaturated hydrocarbons (**b** in the figure; P is a phosphorus atom, Ph an aromatic phenyl group). Light-induced reactions of organometallic tungsten complexes with C–H bonds in aromatic compounds and in silanes — silicon-based equivalents of hydrocarbons — were also observed.

But the field really came alive in the early 1980s, when two groups

reported that iridium from an organometallic complex could be inserted between the atoms of C–H bonds in simple alkanes — the first direct observations of oxidative addition (**c** in the figure; Me is a methyl group, CH₃). Shortly afterwards, lutetium-based C–H activation processes were discovered. These findings led to an explosion in C–H activation research that continues to expand to this day.

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versions of enzymes, because the whole enzyme structure, not just the active site, is often required to provide a selective C–H activation reaction. A few synthetic systems have been generated that use multiply bonded metals to react with hydrocarbons, but these involve metals such as zirconium, titanium and tantalum, which aren't typically found in enzymes. The latest efforts aim to exploit ruthenium and iron as catalytic metals, so mimicking biological systems more closely. Several synthetic iron complexes have been made that use oxygen, or other oxidants such as hydrogen peroxide, to convert alkanes into oxygenated products. These reactions might proceed via transient intermediates that bear Fe–O bonds, but it is difficult to say whether such intermediates are the same as those seen in enzymes because, in most cases, they cannot be easily isolated and characterized.

What other mechanistic questions are there?

Perhaps the biggest issue is whether short-lived alkane complexes, in which C–H bonds bind weakly to metals, act as intermediates in C–H activation reactions that occur by oxidative addition. Direct evidence for this is starting to come from infrared flash kinetics studies, which use rapid laser-pulses to probe reaction intermediates via infrared spectroscopy.

Several groups have detected intermediates with very short lifetimes that have been assigned alkane-complex structures. Liquefied xenon and krypton were used as the ultimate inert solvents in one such study. This enabled data to be obtained that were unswayed by solvent interference with the C–H activation reactions under investigation.

What other ways are there to study these intermediates?

In a brilliant piece of work, alkane-complex intermediates have been detected and characterized at low temperatures using nuclear magnetic resonance spectroscopy. A couple of complexes have even been isolated as solids and characterized by X-ray diffraction, although in these cases the complexes fall apart in solution. All these mechanistic studies provide information that is essential for designing improved C–H activation reactions.

What else needs to be done?

More reactions must be developed, so that C–H bonds can be activated as required in any molecule. Although some useful catalytic C–H activation reactions now exist, few can be applied to a broad range of compounds, and many of these work best in unsaturated molecules. Furthermore, the temperatures required for these reactions are often

inconveniently high, too much catalyst is needed, and the required reagents are often corrosive and/or expensive. Nevertheless, such transformations are routinely used — for example by chemists in the pharmaceutical industry preparing drug candidates — and they will inevitably soon find their way into industrial applications. Effective methods for the catalytic activation of C–H bonds in alkanes are still rare, but there are encouraging signs of progress, such as the rhodium and platinum chemistry described earlier. These reactions, which are unprecedented using classical chemistry, demonstrate the power of C–H activation to unlock the potential of inert hydrocarbons, and tantalize us with the promise of discoveries yet to come.

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FURTHER READING

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