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What is C–H Bond Activation?
Bengü Sezen and Dalibor Sames

1.1
Introduction

The possibility of direct introduction of a new functionality (or a new C–C bond) via direct C–H bond transformation is a highly attractive strategy in covalent synthesis, owing to the ubiquitous nature of C–H bonds in organic substances. The range of substrates is virtually unlimited, including hydrocarbons (lower alkanes, arenes, and polyarenes), complex organic compounds of small molecular weight, and synthetic and biological polymers. Consequently, selective C–H bond functionalization has long stood as a highly desirable goal. The introduction of transition metals to the repertoire of reagents unlocked entirely new opportunities in this area. As such, novel reactions have been discovered and the term “C–H bond activation” has been coined and used to describe certain C–H cleaving processes, initially in the context of saturated hydrocarbons. With time this term has become popular, if not fashionable, and its frequent and liberal usage has led to some uncertainty about its definition and meaning. Complex organic substrates contain a plethora of C–H bonds of different acidity and reactivity, and consequently many mechanistic modes exist for an overall C–H functionalization process (e.g. radical, electrophilic substitution, deprotonation, metal insertion).

Naturally, the question of which processes can be described as “C–H bond activation” arose. After numerous discussions with colleagues in the broad chemical community, we felt compelled to provide some thoughts on this topic, including a historical perspective.

1.2
Activation or “Activation”

In lay language, “activation” means making an object or a person active. A number of fields of science and engineering have adopted this term to describe various processes and phenomena (e.g. regeneration of inorganic catalyst, transformation of inactive enzyme to an active form, excitation by heating or irradiation) [1]. In
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the context of chemical reactions, “activation of a substrate” or “activation of a bond” refers to, in a most general sense, any process or phenomenon by which the reactivity of a substrate or a bond is increased. Thus, this represents a rather open term and as such is used by the chemical community in many different ways and contexts; for instance, activation of bonds by substituents (cf. activated C–H bonds in malonate esters) or activation of bonds by formation of a discrete intermediate between the substrate and a reagent (cf. alkene activation by Lewis acids). Although distinction between “activation” and “reaction” can in principle be made, “bond activation” is frequently equated with bond cleavage. For instance, activation of strong bonds (C–H, C–C, C–F) is often understood as cleavage of these bonds with transition metal reagents. Similarly, “nitrogen activation” describes a variety of processes for reduction of N₂ to hydrazine or ammonia.

In this light, we can appreciate the wide spectrum of interpretations and uses of this terminology. To bring some clarity to our discussion, we first need to make a clear distinction between “activation” and “reaction”. In harmony with the general understanding of the term “activation”, “bond activation” should refer to any chemical process which increases the reactivity of a bond in question (“general definition”) [2]. On the other hand, bond-cleaving processes should be labeled by a separate term, for instance “bond transformation”. We should emphasize that both of these terms, used in this general sense, cast no limits on the actual activation or reaction mechanism.

Nevertheless, in addition to this general understanding of the term, “bond activation” has acquired specific meaning in various subdisciplines. Most notably, “C–H bond activation” is frequently used as an organometallic term to describe certain metal-mediated processes (“organometallic definition”). Before we address this inconsistency, let us first elucidate the origin and historical context of “C–H bond activation” as an organometallic term.

1.3 The Origin and Historical Context of the “Organometallic Definition”

One of the early uses of the “C–H bond activation” term appeared in the chemical literature in 1936 to describe the H–D exchange in methane catalyzed by a heterogeneous Ni⁰ catalyst (Scheme 1) [3]. Although no definition of the term was provided, this work implied that a new mode of chemical reactivity was operative at the metal surface, enabling cleavage of alkane C–H bonds. With some insight, an analogy between this new process and cleavage of a hydrogen molecule on hydrogenation surfaces was proposed.

A few decades later in 1968, Halpern formulated the need for new approaches to the activation of C–H bonds with a particular focus on saturated hydrocarbons. C–H bond activation, equated with “dissociation of carbon–hydrogen bonds by metal complexes”, was identified as one of the most important challenges in catalysis [4]. Perhaps the most influential discovery in this area was made in the late 1960s by Hodges and Garnett, who demonstrated that a homogeneous aqueous so-
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olution of platinum(II) salts catalyzed deuteration of arenes and alkanes [5]. Subsequently, Shilov extended this work by using mixtures of platinum(II) and platinum(IV) salts to achieve hydroxylation and chlorination of alkanes, including methane (Scheme 2) [6]. This work inspired numerous mechanistic studies which established an alkylplatinum species as a reasonable intermediate. Most notably, unusual chemo-selectivity was observed, because rate constants for oxidation of an unactivated methyl group were occasionally greater than those for the oxidation of an alcohol (Scheme 2) [7]. Clearly, a new reactivity mode, other than radical or ionic substitution, had been discovered and the term “activation of saturated hydrocarbons” was used.

\[
\text{CH}_4 + \text{D}_2 \xrightarrow{\text{Ni}(0)-\text{heterogen.}} \text{CH}_3\text{D} + \text{HD} \\
\text{H. S. Taylor, 1936}
\]

Scheme 1

\[
\text{CH}_4 \xrightarrow{\text{K}_2\text{PtCl}_4, \text{CH}_3\text{COOD, D}_2\text{O}} \text{CH}_3\text{D} + \text{HD} \\
\text{Pt(II)/Pt(IV)} \quad \text{(major product!)} \\
\text{H}_2\text{O, 100 °C}
\]

Scheme 2

Transition metal complexes have also unlocked new mechanistic possibilities for cleaving arene C–H bonds. Hydrogen–deuterium exchange at the benzene nucleus, catalyzed by homogeneous metal hydride complexes, was demonstrated by Parshall (Scheme 3) [8]. Interestingly, it was observed that electron-deficient arenes underwent the labeling reaction at faster rates. These results (reaction rates and regioselectivity) were inconsistent with electrophilic substitution; rather, the metal complexes had nucleophile-like properties which pointed to a new mechanism. The intermediacy of arene–metal hydride species, similar to those observed earlier by Chatt and Davidson [9], was proposed (Scheme 3). By analogy with the reaction of alkanes, these new processes were described as “C–H bond activation”, to distinguish them from electrophilic metalation and electrophilic substitution reactions.

Thus, the historical context reveals that the term “C–H bond activation” was introduced with a clear purpose to distinguish metal-mediated C–H cleavage from traditional radical and ionic substitution, and as such was essentially a mechanistic term [8]. As a result we may formulate the “organometallic definition”: the term “C–H bond activation” refers to the formation of a complex wherein the C–H bond
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Equation (1) depicts an early example of an intermolecular addition of an alkane C–H bond to a low valent transition metal complex [12]. Mechanistic investigations provided strong evidence that these reactions occur via concerted oxidative addition wherein the metal “activates” the C–H bond directly by formation of the dative bond, followed by formation of an alkylmetal hydride as the product (Box 1). Considering the overall low reactivity of alkanes, transition metals were able to “make the C–H bonds more reactive” or “activate” them via a new process. Many in the modern organometallic community equated “C–H bond activation” with the concerted oxidative addition mechanism [10b,c].

Strictly speaking, however, in addition to the concerted pathway, oxidative addition can also proceed via radical or ionic mechanisms [13]. Although these alternatives are less likely for alkanes (cf. Eq. 1) they must be considered with substrates containing reactive C–H bonds. For example, proton transfer is a readily available process for acidic C–H bonds (Box 1). Insertion of low valent transition metals has been reported in substrates including alkynes, ketones, and nitriles. As an example, the synthesis of iron hydride complex 5 was accomplished by treating a terminal alkyne with Fe(dmpe)$_2$, generated in situ (Eq. 2). This reaction, assumed to proceed via concerted oxidative addition, stands in stark contrast to deprotonation by a strong base. The label “C–H bond activation” was used to make this distinction and we may argue that it serves well as a qualitative mechanistic term.
Difficulties arise, however, when the organometallic definition is to be applied in a rigorous mechanistic sense. This point is illustrated by comparing the reactions of the iron complex in Eq. (2) with an alkyne or with HCN [14]. Although a metal hydride is the product in both reactions, a significantly faster rate was observed with HCN. This observation suggests that addition of HCN proceeds via proton transfer. Which of these processes can be described as “C–H bond activation”? According to the organometallic definition proton transfer as an ionic pro-
cess would be disqualified. What, however, if oxidative addition proceeds via proton transfer, followed by very fast ion recombination? What if a new experiment suggests that the iron metal interacts with the alkyne triple bond before a proton-transfer step? These questions are often contentious and debated issues and experimental measurements from two different laboratories may favor different mechanistic proposals. This case illustrates the types of problematic issue that arise when attempting to define “C–H bond activation” as a rigorous mechanistic term.

Furthermore, the inconsistency between the restrictive organometallic definition and the general understanding of “bond activation” will pose further problems. Let us discuss this issue in the context of a concrete example – alkyne cupration. It is thought that copper complexation and base-assisted deprotonation work in concert ultimately forming the alkyne cuprate (Eq. 3). Thus, the proposed cupration mechanism may be viewed as a variation of the deprotonation mechanism (π-acid/base-promoted deprotonation)[15]. Experimental evidence shows that CuI salts increase the acidity of the terminal alkyne C–H bond by coordination to the π-bond[16]. Hence, it is clear that copper metal activates the alkyne C–H bond; following the organometallic definition, however, would lead to an absurd linguistic situation; i.e. copper activates the alkyne C–H bond but it is not “C–H bond activation”.

Another instructive scenario may be found when considering the metatlation of arenes. There are two distinct mechanisms for the metatlation of aromatic C–H bonds – electrophilic substitution and concerted oxidative addition (Box 2). The classical arenemercuration, known for more than a century, serves to illustrate the electrophilic pathway whereas the metal hydride-catalyzed deuterium labeling of arenes document the concerted oxidative addition mechanism[8, 17]. These two processes differ both in kinetic behavior and regioselectivity and thus we may appreciate the need to differentiate these two types of process. However, the choice of “C–H bond activation” to designate only one, the oxidative addition pathway, creates a similar linguistic paradox. Indeed, it is hard to argue that the C–H bond in the cationic α-complex is not activated.

These examples clearly illustrate that “bond activation”, whether it refers to C–H bonds or other bonds, is a poor choice for designation of certain reaction types and mechanisms.
1.5 Conclusions

The analysis of the origin and usage of the term “C–H bond activation” revealed dichotomy between the organometallic definition of this term and the general understanding of the word “activation”. As discussed in this essay, “C–H bond activation” is frequently used in the organometallic sense and indeed serves well as a qualitative mechanistic term. Although distinction between the organometallic “C–H bond activation” and general “activation” could be made (and is made intuitively by many), this is clearly degenerate and inconsistent terminology. We have, furthermore, shown that it is difficult to find a rigorous mechanistic basis for defining a “C–H bond activation” class of processes according to the organometallic definition discussed herein.

Consequently, we were faced with the task of formulating a widely acceptable and consistent definition of “bond activation”. Our research, discussions, and analyses led to a conclusion that “bond activation” should refer to a process of increasing the reactivity of a bond in question and as such encompasses an entire spectrum of possible mechanisms. Also, we argue that “activation” is not equivalent to “reaction” or, in other words, that “activation” of a bond is not the same as cleavage of a bond. For the latter process we proposed the general term “bond transformation”. It should be emphasized that both “bond activation” and “bond transformation” are general terms and, therefore, information about the reaction and mechanism category should be specified by additional descriptors (cf. C–H bond arylation via electrophilic metalation, C–H bond metalation via concerted metal insertion).

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References and Notes


2 This view has previously been suggested in print. G. Dyker, J. Heiermann, M. Miura, Adv. Synth. Catal. 2003, 345, 1127–1132. We also thank Professor G. Dyker for sharing his thoughts on this subject.


15 For related zincation of alkenes:


17 Similarly, recent computational studies suggested that the iridium-catalyzed borylation of arenes also proceeded via the insertion mechanism. H. Tamura, H. Yamazaki, H. Sato, S. Sakaki, J. Am. Chem. Soc. 2003, 125, 16114–16126 and references therein.