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Introduction

Abstract Hydrogen is the most abundant element on earth, but only a very small fraction of it is found as molecular gas H_2 . Nevertheless, entire ecosystems are powered by this fuel in nature, raising mankind's hope that sustainable alternatives for the use of fossil fuels exist. Improved systems producing and activating the H_2 molecule have to be developed in order to pave the way for a hydrogen economy, which could satisfy the ever-increasing demand for energy of our society. This chapter provides the theoretical background on the activation of dihydrogen introducing "classical" transition metal-based systems and the so-called frustrated Lewis pairs (FLPs), a class of novel catalysts which has become increasingly popular in the last years. Furthermore, information on a group of naturally-occurring enzymes called hydrogenases is provided. Due to their astonishing high efficiency in producing or activating dihydrogen, hydrogenases are ideal prototypes that could trigger the development of a new era of H_2 activation catalysts featuring unforeseen efficiencies.

1.1 Hydrogen – Fuel of the Future?

In a world as dependent on the availability of energy as ours, the most urgent scientific and technical challenge is to assure a secure and environmentally benign supply of energy.^[1] Facing an ever-increasing demand for energy which currently comprises roughly 16.3 TW per year and which is projected to reach 20 TW in 2030, to double by 2050 and to triple by the end of the century,^[1,2] this challenge represents an enormous problem to solve. Furthermore, a development towards a renewable supply of energy has to occur since only finite resources of fossil fuels are available and combustion of oil, natural gas or coal poses severe problems to the environment and earth's climate by emission of carbon dioxide. And yet, the sun annually provides 100 000 TW of solar energy to our planet, hence only a little more than one hour of sunlight could in principle satisfy our annual energy requirements.^[2] Methods to capture this energy exist but their efficiencies are still insufficient to represent a serious alternative to fossil fuels.

An attractive approach to utilize solar energy is its storage in the form of chemical bonds – like in natural photosynthesis. However, the construction of a so-called “artificial leaf” which is able to efficiently collect and convert solar energy remains an enormous scientific challenge.^[3–5] The hydrogen (H₂) molecule – from organometallic chemists frequently called dihydrogen – is the central energy carrier in an envisioned scenario of alternative energy supplies focusing on sustainable methods to produce, store and consume energy. This aspired scenario has been coined “hydrogen economy”,^[6–8] but problems connected with its realization still persist despite the effort of research already spent on this topic. Accordingly, efficient and sustainable methods to produce H₂ and to recover the energy stored in this molecule have to be developed by the basic science.^[1] In addition to this, novel hydrogen storage materials have to be found in order to guarantee a safe and practical possibility to use dihydrogen as an energy vector, especially in automotive applications.^[9,10] Nevertheless, once the problems are overcome, dihydrogen could be the ideal energy carrier since its energy density is 142 MJ kg⁻¹, which is more than three times larger than that of liquid hydrocarbons.^[9] Furthermore, H₂ is a clean fuel as the only exhaust gas one obtains when burning it with dioxygen is water. A reaction of H₂ and O₂ in a controlled way, for example in a fuel cell, could thus be the key to a sustainable energy supply in the future. However, novel catalysts have to be developed in order to make both the production and energetic exploitation of H₂ more efficient.

Dihydrogen is not only important as a future energy carrier, but even today vast quantities are used in chemical reactions. All crude oil is treated with H₂ within the refining process and hundreds of million tons of ammonia are synthesized every year by the Haber-Bosch process.^[11] A common problem of the presently available methods to achieve these transformations is the fact that often expensive and non-abundant metals as for example platinum have to be used. The main reason for this is the high H–H bond energy of 436 kJ mol⁻¹.^[12] Consequently, reactions involving H₂ usually afford the

input of considerable amounts of energy. Despite this fundamental drawback, catalytic hydrogenations constitute the majority of human-made chemical reactions in the world. Facing the enormous amounts of dihydrogen used in chemical processes, the need for more efficient catalysts becomes even more apparent.

At the present time, nearly all hydrogen gas required for chemical transformations is produced by reactions from carbon feedstocks (fossil fuels and biomass).^[13] The most relevant method is the endothermic steam reforming of methane which is conducted at a nickel catalyst at elevated temperatures and converts natural gas (CH_4 and H_2O) to synthesis gas (CO and H_2). Further amounts of dihydrogen can be obtained by the water-gas shift reaction producing CO_2 and H_2 from CO and H_2O .^[13] It is important to note that this industrial production of dihydrogen is not sustainable since fossil fuels are used to generate H_2 . In a long-term view, energetically unfavored splitting of water by electrolysis or solar power has to evolve into an attractive alternative to steam reforming processes in order to produce H_2 in a sustainable way. However, a massive effort of scientific research is still required in order to improve existing dihydrogen-producing systems. Inspiration for these novel catalysts might come from naturally occurring enzymes (see section 1.4).

1.2 Basic Principles of Dihydrogen Activation

The activation of small molecules like dihydrogen is most commonly conducted at transition metal centers since the availability of d orbitals allows for a variety of possible orbital interactions, ultimately leading to the activation of chemical bonds.^[14] The tuneability in terms of electron configuration and oxidation state are further advantages of transition metals in catalytic reactions. Soon after the discovery of the first metal complex containing a dihydrogen ligand, $\text{W}(\text{CO})_3(\text{P}^i\text{Pr}_3)_2(\eta^2\text{-H}_2)$, by Kubas *et al.* in 1984,^[15] the theoretical foundation for understanding bond formation with a hydrogen molecule was laid. This led to a reinvestigation of known dihydride complexes and soon further dihydrogen complexes appeared in literature.^[16] As an extension of the Chatt-Dewar-Duncanson model for complexes with unsaturated alkene or alkyne ligands (“ π -complexes”), the bonding situation found in H_2 complexes has been termed “ σ -complex”, indicating that a σ bond interacts with a metal center.^[17] Analogous to the three-center two-electron (3c-2e) bonding in carbocations and boranes, this binding can be called nonclassical.^[16] The set of possible orbital interactions of a transition metal M with the typically *side-on* coordinated H_2 molecule is depicted in Figure 1.1. In principle two synergistic orbital interactions, donation of electron density from the bonding σ orbital of dihydrogen into a vacant d orbital (d_{z^2}) of the metal and $\text{M} \rightarrow \text{H}_2$ backdonation into the antibonding σ^* orbital, contribute to an overall binding interaction.

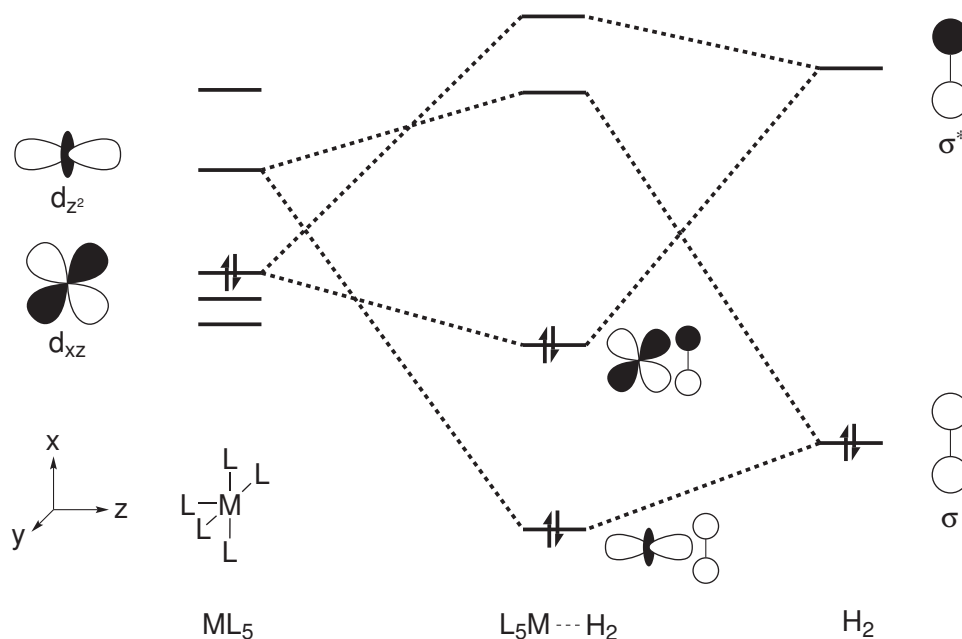


Figure 1.1. Orbital interactions in an octahedral $M-H_2$ σ -complex with a *side-on* coordinated dihydrogen ligand. Adapted with permission from Kubas *et al.*,^[18] © 2007 American Chemical Society.

Homolytic and Heterolytic Splitting of H_2

Considering backdonation of metal d electrons into the antibonding H_2 orbital is not only crucial to the understanding of the stabilization of a metal- H_2 σ -complex, in fact it is also the key to comprehend activation of the H-H single bond. If the electron density donated into the σ^* orbital is large enough, the H-H bond is cleaved homolytically and a dihydride complex is formed. However, no sharp separation between H_2 and dihydride complexes exist, but rather a continuum of different H-H bond distances (Figure 1.2). The elongation of the H-H bond depends (analogously to the degree of olefin activation described by the Chatt-Dewar-Duncanson model) on the degree of backdonation from the metal center.^[16] Astonishingly, the very strong H-H bond can be stretched to more than twice its length in molecular H_2 during its activation at a metal center. Powerful methods to probe the degree of activation of the H_2 molecule in metal complexes are neutron diffraction and nuclear magnetic resonance (NMR) spectroscopy, permitting a direct determination of the H-H bond distance and, respectively, the measurement of coupling constants J_{HD} in HD-substituted complexes or T_1 relaxation times.^[18]

The type of bond activation associated with a high degree of backdonation of electron density into the H_2 σ^* orbital culminates in a homolytic splitting of the dihydrogen molecule. By this, the oxidation state of the metal increases by two and overall an oxidative addition takes place. Furthermore, the total coordination number of the complex increases by one. On the contrary, neither the oxidation state of the metal nor the coordination number changes when a heterolytic cleavage of the dihydrogen molecule

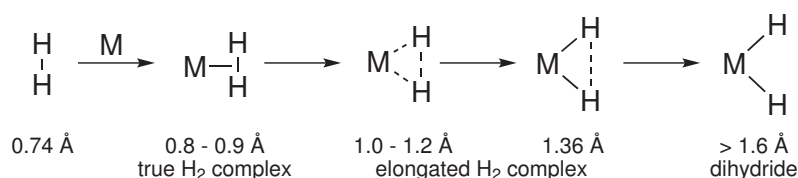


Figure 1.2. Stretching of H–H bond distances for a series of M–H₂ complexes. Adapted with permission from Kubas *et al.*,^[16] © 2001 Elsevier.

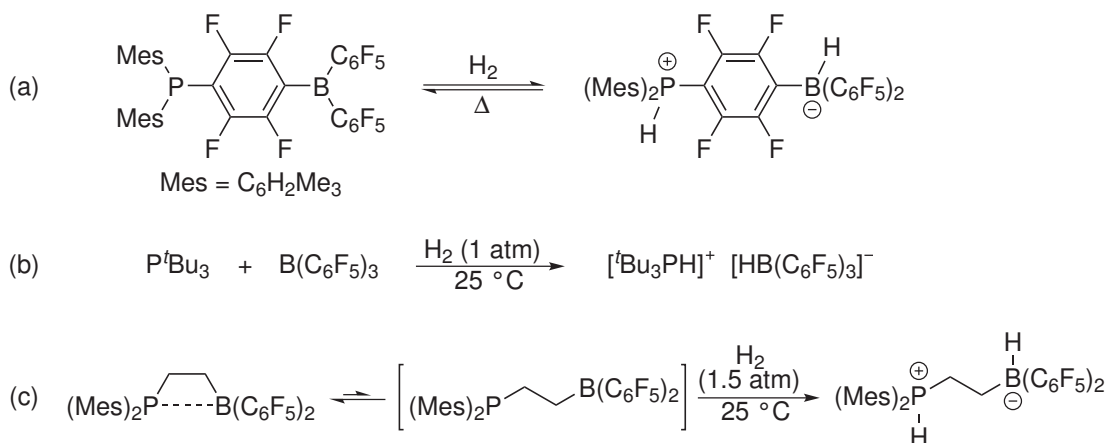
occurs. In this case the H–H bond is not split into equal parts, but formation of a hydride ion (H[−]) and a proton can be observed. Typically the hydride ion coordinates to the metal center (thereby decreasing the overall charge of the complex by −1) and the remaining proton is accepted by an internal or external base.^[19] Whether a homolytic or heterolytic splitting of the H₂ molecule occurs, is governed by the electronic properties of the complex. Electron-rich metal centers favor the homolytic cleavage since the extent of backdonation is typically relatively large, whereas electron-poor/electrophilic metals mostly show heterolytic cleavage of H₂. Here, backdonation is weak and most of the overall bonding interaction can be attributed to a strong H₂→M σ-donation.^[16,18] In such complexes, the H₂ molecule is usually highly polarized. Indeed, coordinating H₂ to a highly electrophilic cationic metal usually leads to an increase of its acidity by up to several orders of magnitude.^[18] Once H₂ is homolytically or heterolytically activated, protons and/or hydride ions can be transferred to a substrate, providing the basis for a large array of homogeneous industrial processes. Metal complexes which have been successfully applied in large-scale industrial catalytic hydrogenations include such prominent examples as Wilkinson’s rhodium-based catalyst RhCl(PPh₃)₃ or the ruthenium-based Noyori systems.^[20,21]

1.3 Frustrated Lewis Pairs (FLPs)

Until relatively recently in the history of dihydrogen activation, chemists assumed that only transition metals were able to cleave the very stable H–H bond. This belief was fundamentally shattered when a series of metal-free systems were discovered at the beginning of the 21st century. Bertrand *et al.* reported that stable singlet carbenes can mimic to some extent the reactivity of transition metals by nucleophilically activating dihydrogen or even ammonia under very mild conditions.^[22] Even more groundbreaking was the development of the concept of frustrated Lewis pairs (FLPs) which was popularized by the groups of Stephan and Erker.^[23–27] The discovery of a phosphine-borane that was able to reversibly activate dihydrogen by Stephan *et al.*^[28] in 2006 and subsequent publication of related intermolecular^[29] and intramolecular^[30] systems paved the way for a new era of hydrogen activation already foreshadowing unforeseen applications.^[31]

1.3.1 General Concept

The first systems represented in Scheme 1.1 had in common that an electron-deficient borane was combined with a Lewis basic phosphine. Contrary to the widely accepted understanding that combination of a Lewis acid and a Lewis base would inevitably lead to the formation of a Lewis acid–base adduct, the reactivity inherent to FLPs was not quenched by adduct formation. Instead, steric constraints prevented the system from forming unreactive adducts and enabled the use of FLPs for bond activation. The first intramolecular system^[28] (example (a) in Scheme 1.1) was shown to reversibly incorporate dihydrogen. The Lewis acidic borane accepts a hydride ion and the phosphine Lewis base is protonated to yield a zwitterionic phosphonium borate. Hence the H₂ molecule is cleaved heterolytically. Further studies led to the discovery of the FLP shown in Scheme 1.1 (b). Here, a combination of B(C₆F₅)₃ and tri-(*tert*-butyl)phosphine afforded an FLP which could activate dihydrogen under mild conditions.^[29] The group of Erker developed the linked FLP shown in example (c) of Scheme 1.1, which could also achieve a metal-free activation of H₂ despite interaction of the phosphine and borane moieties.^[30,32] In solution, rupture of the weak P⋯B bond gives the intramolecular FLP which was also shown to be suitable for H₂ activation. From a thermodynamic view, intramolecular FLPs have several advantages since the critical step in the thermodynamic cycle, the association of the reaction partners, involves a considerable loss of entropy in the case of intermolecular systems.^[33,34] For this problem, the notion “termolecularity trap” has been used.^[35]



Scheme 1.1. Several frustrated Lewis pairs and their reactivity with H₂: (a) First FLP published by Stephan *et al.*,^[28] (b) an intermolecular^[29] and (c) a second intramolecular^[30] system.

The prospect of a hydrogenation catalysis no longer dependent on expensive and toxic metals led to an increased scientific interest in this particular field of research. Consequently, the insights into this fascinating topic grew rapidly and were summarized several times.^[23,27,36–38] In the course of further uncovering FLP reactivity, the early systems were modified and it was soon realized that the concept of frustrated Lewis

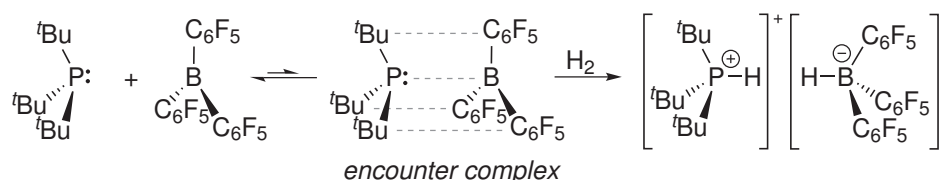
pairs was suitable to describe the activation of dihydrogen by a number of other systems. However, most modifications targeted the Lewis basic component and it was demonstrated that also nitrogen bases^[23,39] and N-heterocyclic carbenes (NHCs)^[40–44] were able to assist in the heterolytic cleavage of H₂. On the contrary, the borane Lewis acid was not subjected to much variation since this mostly lowered the reactivity of the obtained systems.^[45–47] Only few systems were reported that did not involve boranes with strongly electron-withdrawing substituents for FLP-type chemistry.^[48–52] A relatively recent development in this respect is the utilization of aluminum in FLP-type chemistry. These compounds show interesting properties and can be used in the activation of organic and inorganic molecules.^[53–64]

When developing novel FLP systems it is important to consider the dual importance of optimizing structural and electronic features of both the Lewis acid and the Lewis base.^[65,66] On the one hand, the reaction partners should have bulky residues in order to prevent the formation of simple Lewis adducts, and on the other hand the cumulative acid–base strength of the system should be high enough to enable the heterolytic cleavage of H₂.^[33] In principle it is possible to use a relatively weak Lewis base, but this requires a very electron-deficient Lewis acid as counterpart which is normally achieved by incorporating particularly electron-withdrawing substituents. By careful adjustment of steric (principle of “size exclusion”)^[66] and electronic^[67,68] properties it is also possible to add chemoselectivity or functional group tolerance to the system.

Besides dihydrogen also various other substrates have been used in reactions with FLPs. Particularly important is the activation of CO₂^[69–74] as it represents a potent greenhouse gas and simultaneously a sustainable source for the production of basic chemicals (e. g. carboxylic acids, methanol).^[75] Furthermore, FLPs were found to activate other small molecules such as THF,^[23] CO,^[76–78] alkenes,^[79] alkynes,^[80] silanes,^[81] halogens,^[82] N₂O,^[83–86] NO^[87,88] and SO₂.^[89] Even activity in polymerization reactions has been demonstrated for FLP systems.^[90,91] Besides this, FLP chemistry has now reached the point where it becomes interesting also for organic chemists and the chemical industry because FLP-based catalysts can be used for the transformation of organic substrates. In fact, a number of metal-free catalytic hydrogenations have been developed and are now available for reactions performed under mild conditions including substrates as imines,^[92] nitriles,^[92] aziridines,^[92] alkenes,^[93,94] alkynes,^[95] N-based heterocycles^[96] and many more. FLP catalysts have been optimized for hydrogenation reactions and surprisingly simple systems including for example ethers as Lewis bases have been developed.^[97] Even more astonishingly, first attempts to implement chirality have been successful and it was found that chiral FLPs can be used in asymmetric hydrogenations.^[98] Hydrogenation reactions mediated by FLPs have been comprehensively summarized recently.^[99–101]

1.3.2 Mechanism of H₂ Activation in FLPs

Despite a considerable amount of scientific contributions to this field, the mechanism of H₂ activation mediated by FLPs still remains a matter of debate. In their first publication on this topic,^[28] Stephan *et al.* speculated that the heterolytic splitting of dihydrogen might be initiated by *side-on* coordination of H₂ to the boron center and subsequent addition of H₂ to the B–C bond prior to reaction with the Lewis base. However, calculations showed that the activation barrier for such adduct formation in FLPs is rather high^[102,103] and no experimental proof for an interaction of boron with H₂ was found.^[29] Consequently, coordination of H₂ to the boron Lewis acid can be considered rather unlikely. In addition to *side-on* coordination to the boron center, also *end-on* coordination to the phosphine Lewis base was proposed based on the observation of phosphine-hydrogen adducts in low-temperature matrix-isolation experiments.^[104,105] However, the adducts were extremely unstable. The most probable mechanism of heterolytic H₂ splitting in phosphine-borane FLPs is represented in Scheme 1.2 and has been originally proposed by Pápai *et al.* in 2008.^[102] Instead of forming unreactive Lewis acid–base adducts, the two components of an FLP exhibit secondary interactions which lead to a weak association. In such an “encounter complex” the prevailing interactions are H⋯F interactions which is in line with the earlier observation of attractive dispersion forces in phosphine-borane addition products.^[106] Very recently, in addition to highly sophisticated computational investigations,^[107] even experimental proof for the association *via* weak dispersion interactions has been obtained by means of NMR spectroscopy.^[108]



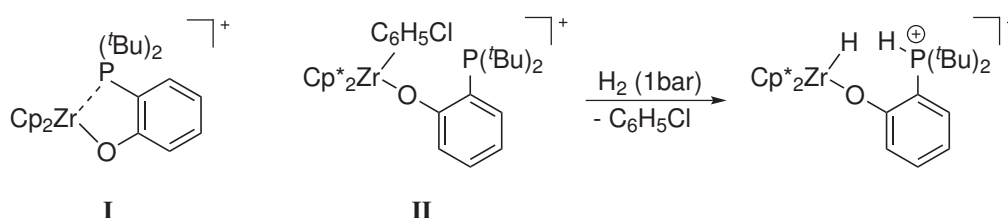
Scheme 1.2. Most probable mechanism of hydrogen splitting mediated by FLPs. Formation of a loosely bound encounter complex precedes the actual H₂ splitting step.

After formation of the encounter complex, the H₂ molecule enters the system and interacts with both reactive centers of the FLP. The true nature of this interaction is still under debate, but the signs increasingly point to a polarization of the H₂ molecule as part of the shifting of electron density from the phosphine to the boron center. In the course of this shifting, the H₂ σ* orbital accepts electron density from the phosphine and simultaneously electron density is donated from the H₂ σ orbital to the electrophilic borane. Consequently, the H–H bond is weakened and ultimately cleaved in a concerted way resulting in the formation of the phosphonium borate.^[102,109] In the transition state, a non-linear arrangement of the H₂ molecule has been found by structural and theoretical studies.^[110,111] A second concept has been proposed by Grimme *et al.* in 2010.^[112]

According to this model, a transfer of electrons is not necessarily required in order to activate dihydrogen. Instead, the electric field generated by the donor and acceptor atoms of the FLP might be sufficient for polarizing the H₂ molecule and finally leads to the observed heterolytic cleavage of dihydrogen. However, a number of subsequent theoretical calculations found only small contributions of the polarization effect to the overall interaction energy.^[113,114] Indeed, Pápai *et al.* recently showed in a comparative study that the electric field theory can be seriously questioned.^[115] Hence it can be assumed that H₂ activation in FLPs is the result of orbital interactions which involve the shifting of electron density.

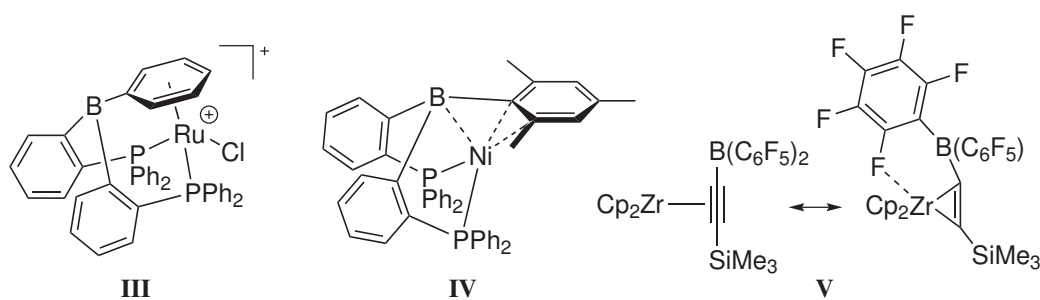
1.3.3 Transition Metal-Based FLPs

Still in its infancy, frustrated Lewis pair chemistry has not focused much on transition metals since scientists were eager to develop main group alternatives for transition metal-based catalysts. Nevertheless, indications that the FLP concept is also important in the realm of transition metal chemistry got stronger especially in the last few years. Indeed, FLP-type reactivity represents an exiting approach to achieve novel activation pathways and reactivity patterns in transition metal chemistry. Of high importance in this field were the contributions of Wass *et al.* demonstrating that some early transition metals are able to act as Lewis acids in FLP-type chemistry.^[116] The cationic zirconocene-phosphinoaryloxy complex **I** depicted in Scheme 1.3 showed for example reactivity in the dehydrogenation reactions of amine boranes. The related chlorobenzene adduct of the pentamethylcyclopentadienyl derivative **II** could even cleave the dihydrogen molecule.^[117] In general, these two and other systems developed by the group of Wass were shown to react for example with H₂, CO₂, CO, amine boranes, alkenes, alkynes, ethers or acetone and thus they represent “typical” FLPs, at least concerning their reaction pattern.^[116,118] Not only did these systems show a markedly higher reactivity than classical main group FLPs in many cases, additionally they featured unprecedented reactivities as for example CO reduction or C-halide cleavage in alkyl halides.^[118] Today also neutral or cationic lanthanum,^[118] titanium^[119,120] or hafnium complexes^[120] showing FLP reactivity are available. A comprehensive review about this chemistry has appeared recently.^[116,121]



Scheme 1.3. Zirconocene-phosphinoaryloxy complexes featuring FLP-type chemistry (Cp = C₅H₅, Cp* = C₅Me₅).^[117]

Expanding the FLP concept to the group of transition metals was an intriguing approach and soon other examples appeared in literature. However, most of the systems were restricted to electron-deficient transition metal centers as exemplified by further scandium-,^[122–124] zirconium-,^[125–128] hafnium-,^[129] ruthenium-,^[130] platinum-,^[131] or zinc-based^[132] complexes. A different approach to incorporate transition metals also makes use of the Lewis acidity of metal centers and their ability to facilitate a nucleophilic attack at a coordinated ligand. An example in which the metal fragment acts as a mere bystander was recently reported by Stephan and co-workers, demonstrating that complex **III** in Scheme 1.4 readily accepts a hydride ion at the phenyl ring when a phosphine base and H₂ are added.^[133] Such ancillary transition metal centers are not directly involved in the FLP reaction itself, but they are nevertheless essential for creating the actual Lewis acidic center. In addition to this, also cases are known in which the (still Lewis acidic) metal center assists in the formation of the carbon-based Lewis base, for example in ruthenium acetylides.^[134] On the contrary, in some other exemplary cases, the metal fragment is the substrate (transformations occur in the ligand sphere) or provides only the structural framework for activation.^[135]



Scheme 1.4. Examples for transition metal complexes showing FLP-type reactivity.

In contrast to Lewis acidic metal centers, Lewis basic transition metal fragments appear only rarely in literature, although the topic of metal-only Lewis pairs including transition metal Lewis bases was addressed recently by a review focusing on metal-metal dative bonding.^[136] In FLP-type chemistry, transition metal Lewis bases did not play a decisive role until now. However, some examples already exist where the metal fragment shows a Lewis basic character. The potential of certain platinum complexes^[137] to act as Lewis bases in reactions with fluoroboranes was recently demonstrated and furthermore also rhenium hydride/borane FLPs in which the metal hydride is the Lewis base were published.^[138] A promising concept to achieve Lewis basicity directly at the transition metal center is to incorporate boranes as ligands in the environment of the metal.^[139] Complex **IV** in Scheme 1.4 featuring close interactions with the boron atom and two carbon atoms of the mesityl ring for example cleaves H₂ heterolytically. In the course of the reaction the hydride ion is accepted by the borane yielding a bridging B–H–Ni hydrido ligand and the nickel center gets protonated.^[140] Furthermore, an intramolecular boron Lewis acid/zirconocene pair with a weak Zr...F contact (compound **V** in Scheme 1.4) was reported to react with a variety of small molecules.^[141,142]

As has been pointed out by Owen,^[139] many metal-borane complexes are not “frustrated” in the original sense since in most cases a direct bonding interaction between metal and borane moiety exists. This aspect is a general problem when talking about transition metal FLPs since – as seen above – also many ligand-assisted reactions at metal centers involving internal bases can be regarded as FLP-type transformations.^[121] In analogy to the known cooperative effects in transition metal catalysis, these systems have been termed “cooperative Lewis pairs” by Wass and co-workers due to the absence of steric factors preventing adduct formation.^[121] Indeed, in many cases H₂ cleavage by transition metal FLPs and ligand-assisted hydrogenation reactions are not so easily categorized and intermediate cases exist.^[116] Nevertheless, keeping the FLP concept in mind when considering such systems is useful since it permits a new view on already existing catalysts and could lead to their improvement. While the pool of transition metals offers new possibilities to extend the set of Lewis acids and Lewis bases in FLP-type reactions, the boundaries between “classical” FLP chemistry and cooperative activation by metals and ligands become increasingly blurred. Carrying FLP chemistry to extremes by expanding the concept to transition metals, might lead to interesting new developments in catalysis.

1.4 Hydrogenases – The Natural Hydrogen Economy

Despite the many efforts already made, establishing a sustainable energy supply including dihydrogen as the primary energy carrier still remains an enormous challenge. Efficient ways to produce, store and activate the H₂ molecule have to be found in order to replace fossil fuels as driving force of our society. In this respect nature is already far ahead of our development since the estimated global amount of dihydrogen produced and consumed in nature adds up to roughly 0.3 billion tons per year.^[143] Invariably, the concentrations of H₂ encountered by microorganisms are extremely low and therefore the enzymes involved in its metabolism feature high affinities and efficiencies. Indeed, dihydrogen is a valuable energy source or a sink of redundant electrons for many anaerobic or – less frequently – aerobic microorganisms with diverse metabolisms.^[144,145] Among those microorganisms engaged in H₂ metabolism are mainly bacteria and archaea, but also some eukaryotes.

Most of the processes consuming or producing dihydrogen are performed by an ancient group of enzymes named hydrogenases which catalyze the reversible reaction $\text{H}_2 \rightleftharpoons \text{H}^+ + \text{H}^- \rightleftharpoons 2\text{H}^+ + 2\text{e}^-$.^[146,147] From the isotope exchange reaction $\text{H}_2 + \text{D}_2\text{O} \rightleftharpoons \text{HD} + \text{HDO}$ it was inferred that hydrogenases cleave the H₂ molecule in a heterolytic way.^[148] According to the metal content of the active site, hydrogenases can be classified into [FeFe], [NiFe] or [Fe] hydrogenases. Although the three types of hydrogenases represent phylogenetically distinct classes,^[145] a unifying structural motif for activation or production of H₂ can be recognized in the enzymes since all of them harbor Fe^{II} metal ions in their active sites.^[143,149,150] Another common feature

is the presence of highly toxic CO or CN⁻ ligands which were previously considered completely abiological.^[151] Even though the reversible formation of H₂ from protons and electrons looks like a simple reaction, its realization is not so easily achieved since the standard redox potential $E^\circ(\text{H}_2/\text{H}^+)$ amounts to -414 mV at pH 7, a value below the potential of common redox mediators.^[152] This is why highly specialized enzymes with complex active centers are necessary to mediate the reaction. Facing the astonishingly high efficiencies of these biological systems, scientists try to discover the general concepts behind H₂ activation and to develop novel catalysts inspired by nature.^[143,153,154] As a consequence of the rapid developments in the field especially within the last two decades, a number of general reviews covering the most diverse aspects of hydrogenases such as their structure and function,^[146,147,150,155–157] occurrence and classification,^[145,158] physiological^[152,159] and chemical aspects,^[151,160,161] synthetic model compounds,^[149,162,163] computational studies,^[164] O₂ tolerance,^[165,166] biosynthesis,^[167] and electrocatalytic properties^[168,169] appeared in the literature. Very recently, an extensive review covering the different facets of hydrogenases was published.^[170] The following sections summarize the essential characteristics of the three classes of hydrogenases before focusing on approaches to design novel catalysts reminiscent of the naturally occurring systems.

1.4.1 [FeFe] and [NiFe] Hydrogenases

The first bacterial enzyme capable of activating molecular hydrogen was already observed in 1931 and coined “hydrogenase” by Stephenson and Stickland.^[171] However, the interest in this particular class of enzymes did not start to intensify until the 1990s after the publication of the first crystal structures of [FeFe] and [NiFe] hydrogenase enzymes.^[172–174] Subsequently, the significance of hydrogenase enzymes for the development of future H₂ production or activation catalysts was recognized and publications in this field increased rapidly.

Although, in principle, all hydrogenases work bidirectionally as isolated enzymes, the situation does not represent a true equilibrium process in living organisms because the physiological conditions provided by the cell mostly decide on the preferred direction of the reaction.^[170] [FeFe] hydrogenases preferentially catalyze the formation of dihydrogen from protons and electrons, whereas [NiFe] hydrogenases are mainly found in organisms performing the oxidation of H₂.^[175] Extremely high activities for H₂ generation are found in [FeFe] hydrogenases, but the enzymes only work under strictly anaerobic conditions.^[165,175] Under optimum conditions for example a single [FeFe] hydrogenase enzyme from *Desulfovibrio desulfuricans* is able to produce 9000 molecules of H₂ per second at 30 °C.^[175,176] In contrast to [FeFe] hydrogenases, [NiFe] hydrogenases are not irreversibly destroyed by O₂ and some variants are even active under aerobic conditions.^[165] However, the activity of [NiFe] hydrogenases is usually lower.

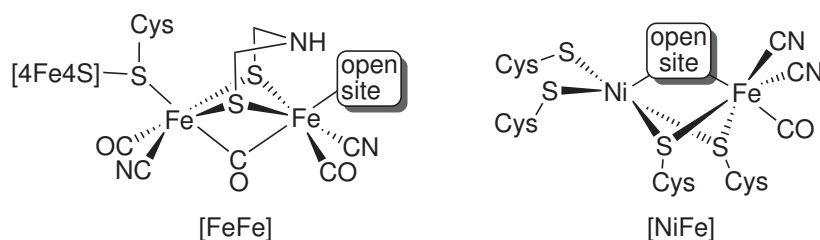


Figure 1.3. Structures of the active sites of [FeFe] and [NiFe] hydrogenases.^[159]

Figure 1.3 depicts the structures of the active sites of [FeFe] and [NiFe] hydrogenases. First indications of the presence of toxic CO and CN⁻ ligands obtained by IR spectroscopy^[177] startled the scientific community and established an astonishing connection between the chemistry of hydrogenases and traditional organometallic chemistry.^[18,151] Because of their high sensitivity towards dioxygen, these organometallic centers normally lie deeply buried within the protein scaffold and pathways for the transport of reactants and products as well as for electrons are necessary.^[170]

[FeFe] Hydrogenases

Most [FeFe] hydrogenases are monomeric and consist of a single catalytic subunit only.^[145] The active site shown in Figure 1.3 is also called “H-cluster” and consists of two iron atoms which are bridged by a CO molecule and a dithiolate ligand containing an amino group. Each of the two metals is further coordinated by a CN⁻ ligand and an additional CO molecule. The so-called proximal iron atom is linked to a [4Fe4S] cluster *via* a bridging cysteine (Cys) sulfur ensuring a pathway for electron transport. The distance of the proximal iron to the [4Fe4S] cluster amounts to approximately 4 Å. The other iron atom – the so-called distal iron atom – is believed to be the binding site of inhibitors like CO or O₂, as well as of dihydrogen. In the history of exploring [FeFe] hydrogenase activity, there has been some considerable debate on the identity of the bridgehead atom of the dithiolate ligand. Meanwhile, strong experimental and theoretical evidence confirms the presence of an NH group rather than the presence of the previously proposed oxygen atom or CH₂ group.^[178–181] By accepting or donating a proton, the NH group plays an important role in the catalytic cycle.^[170] Considering that the [4Fe4S] cluster might be present in its oxidized [4Fe4S]²⁺ or reduced [4Fe4S]⁺ form and that the binuclear part has three possible redox states (Fe^{II}Fe^{II}, Fe^IFe^{II}, Fe^IFe^I), a total of six redox states are imaginable for the H-cluster.^[170] However, not all of these redox states actually occur under physiological conditions. Most probably, the H_{ox} ([4Fe4S]²⁺–Fe^{II}Fe^I) and the H_{red} ([4Fe4S]²⁺–Fe^IFe^I) states are essential components of the catalytic cycle.^[146] Recently, a super-reduced state H_{sred} ([4Fe4S]⁺–Fe^IFe^I) has been identified^[182] and considered as part of the catalytic cycle.^[170,183]

In the quest for biomimetic catalysts, an impressive number of structural and functional models for the [FeFe] hydrogenase has been designed and especially in the last few

years an extremely high level of sophistication has been reached.^[170] A recent example of a complete [FeFe] hydrogenase model is described in section 1.5.^[184] Besides the general reviews cited above, some additional review articles exist which exclusively treat the [FeFe] hydrogenase and its model compounds.^[185–189]

[NiFe] Hydrogenases

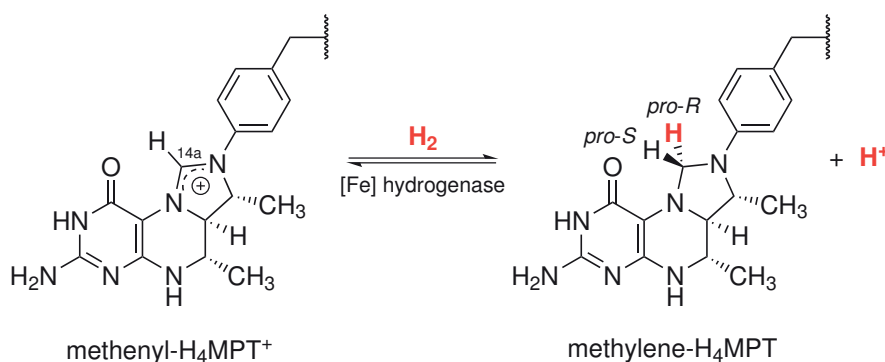
In contrast to mostly monomeric [FeFe] hydrogenases, almost all [NiFe] hydrogenase enzymes consist of a large subunit harboring the active site, and a small subunit accommodating the iron-sulfur (FeS) clusters of the electron transport chain.^[174] Different hydrophobic gas channels^[190] and proton transfer pathways have been identified in [NiFe] hydrogenases.^[170] The active site of standard [NiFe] hydrogenases (Figure 1.3) consists of a nickel and an iron atom which are bridged by two cysteine sulfur atoms. Furthermore, the Ni center is coordinated by two additional cysteine residues and the Fe center features two CN⁻ and one CO ligand. In a distance of approximately 11 Å to the redox active Ni atom, a [4Fe4S] cluster is located which belongs to the small subunit of the enzyme and takes care of the transport of electrons.^[170] In certain oxygen-tolerant [NiFe] hydrogenases the proximal FeS cluster is not a [4Fe4S] cluster but a unique [4Fe3S] cluster.^[191–193] The possibility of this cluster to access a superoxidized state and to deliver two electrons back to the active site in order to reduce O₂ is assumed to be the reason for the retention of hydrogenase activity even in the presence of dioxygen.^[191–198] The so-called [NiFeSe] hydrogenases are a subclass of [NiFe] hydrogenases in which one of the terminal cysteine residues coordinating the Ni atom is replaced by a selenocysteine. In comparison to “normal” [NiFe] hydrogenases, these enzymes usually exhibit a significantly higher catalytic activity.^[199]

The catalytic cycle performed by [NiFe] hydrogenases has been the subject of intense debate and in the course of its exploration more than ten different states or intermediates of the active site have been identified.^[200] The main differences between these structures relate to the oxidation state of nickel (Ni^I, Ni^{II} or Ni^{III}) and the nature of the ligand occupying the open coordination site in Figure 1.3. However, in principle only three states possess a special relevance for the catalytic cycle: In the active state of the enzyme, the so-called Ni-SI_a state, no additional bridging ligand exists and the open site remains empty. The oxidation states of the metals are Ni^{II}Fe^{II}. Heterolytic splitting of H₂ yields several different Ni-R states carrying a hydride ion in the bridge between the Ni^{II} and the Fe^{II} centers. The proton is attached to the sulfur of a terminal cysteine residue. Release of this proton and an electron leads to the formation of the paramagnetic Ni-C state still featuring a hydride bridge and a Ni^{III}Fe^{II} oxidation state. Finally, the catalytic cycle is closed by removing the second proton and electron.^[170,200] Also in the case of [NiFe] hydrogenases, great progress in modeling the structure and reactivity of the natural systems has been achieved in recent years and meanwhile also a remarkable functional model of the [NiFe] hydrogenase has been synthesized (see

section 1.5).^[201] A few specialized reviews document the rapid developments in the field.^[202–205]

1.4.2 The [Fe] Hydrogenase – A Novel Kind of Hydrogenase

[Fe] hydrogenase – systematically named H₂-forming methylenetetrahydromethanopterin dehydrogenase (Hmd) – differs from the other two types of hydrogenases in the fact that it does not contain any nickel or iron-sulfur clusters. Furthermore, the enzyme does not catalyze the formation of dihydrogen from protons and electrons or the oxidation of H₂. Instead, it promotes the reversible hydride transfer from H₂ to N⁵,N¹⁰-methenyltetrahydromethanopterin (methenyl-H₄MPT⁺) yielding N⁵,N¹⁰-methylenetetrahydromethanopterin (methylene-H₄MPT) and a proton. Contrary to [FeFe] and [NiFe] hydrogenases, a direct transfer of electrons is not observed in the [Fe] hydrogenase. The reaction is an important step in the production of methane from CO₂ in many methanogenic archaea.^[159,206] The transfer of a hydride ion occurs stereospecifically to the *pro-R* side of the substrate at carbon atom C^{14a} which is derived from CO₂ (Scheme 1.5).^[207]



Scheme 1.5. Stereospecific hydride transfer from H₂ to methenyl-H₄MPT⁺ catalyzed by [Fe] hydrogenase.

Since its discovery in 1990,^[208,209] the understanding of [Fe] hydrogenase has experienced substantial breaks. Indeed, the enzyme was initially believed to be a purely organic hydrogenation catalyst and it took quite some time until the crucial role of an iron-based cofactor was recognized in 2004.^[210] Nevertheless, the prospect to discover novel concepts of H₂ activation fueled the curiosity of the scientific community and meanwhile even details on for example the biosynthesis of the [Fe] hydrogenase are available.^[211–213] A series of reviews represents the cornerstones of the evolution that took place in the understanding of [Fe] hydrogenase.^[214–219]