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Published in:
Chemistry: A European Journal

DOI:
10.1002/chem.201806351

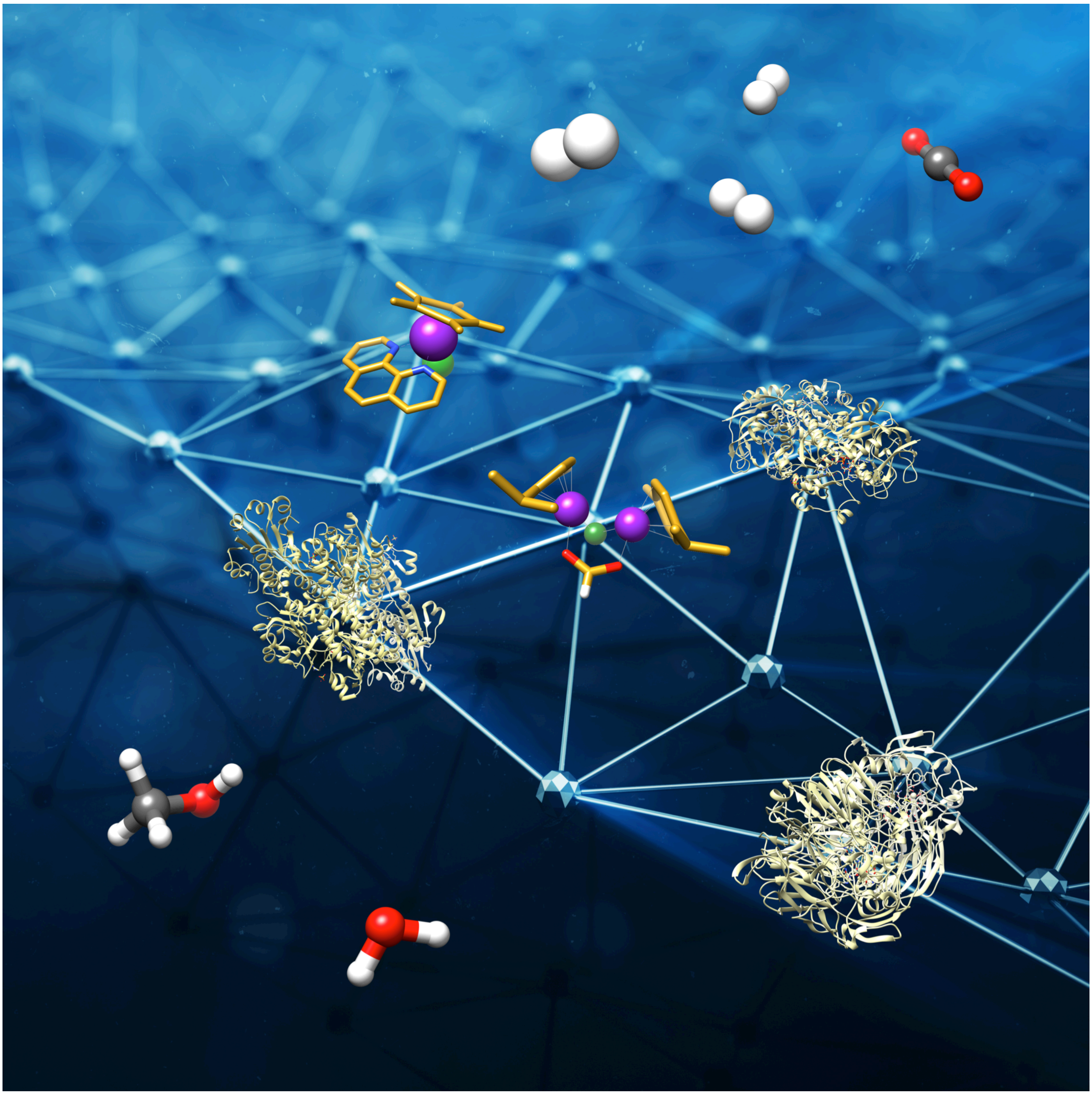
Publication date:
2019

Document Version
Peer reviewed version

Citation for published version (APA):
Tavakoli, G., Armstrong, J. E., Naapuri, J. M., Deska, J., & Prechtl, M. H. G. (2019). Chemoenzymatic Hydrogen Production from Methanol through the Interplay of Metal Complexes and Biocatalysts. *Chemistry: A European Journal*, *25*(26), 6474-6481. https://doi.org/10.1002/chem.201806351

Chemoenzymatic Hydrogen Production from Methanol Through the Interplay of Metal Complexes and Biocatalysts

Ghazal Tavakoli,[a] Jessica E. Armstrong,[a] Janne M. Naapuri,[b] Jan Deska[b]* and Martin H. G. Prechtl[a]*



Abstract:

Microbial methylotrophic organisms can serve as great inspiration in the development of biomimetic strategies for the dehydrogenative conversion of C_1 molecules at ambient conditions. In this concept article, we give a concise personal perspective on the recent advancement in the field of biomimetic catalytic models for methanol and formaldehyde conversions, in presence and absence of enzymes and co-factors, towards the formation of hydrogen at ambient conditions. In particular, formaldehyde dehydrogenase mimics have been introduced in standalone C_1-interconversion networks. Recently, coupled systems with alcohol oxidase and dehydrogenase enzymes have been developed as well for *in situ* formation and decomposition of formaldehyde and/or NADH/NAD^+. Although C1 molecules are already used in many industries for hydrogen production, these conceptual bio-inspired low-temperature energy conversion processes may lead one day to more efficient energy storage systems enabling renewable and sustainable hydrogen generation for hydrogen fuel cells at ambient conditions using C_1 molecules as fuels.

Introduction

Today, overpopulation and overexploitation of fossil fuels have resulted in a strong increase in atmospheric CO_2 resulting in many environmental challenges and these apparent problems will keep gaining impact over the upcoming years. Chemical sciences are therefore asked to bring forward new discoveries and modern approaches to resolving the worldwide demands for renewable and green energy resources. In this context, hydrogen has been deemed to be the best alternative energy source due to its high gravimetric energy density (120 MJ kg^{-1}), non-toxicity, renewability and proven applications in fuel cells. Despite its obvious advantages, hydrogen production and storage have still many difficulties mainly in regard to hydrogen storage and its transportation. Owing to its gaseous nature, dihydrogen exhibits a low volumetric energy density at ambient pressure. Similarly, the handling of hydrogen at elevated pressures in heavy gas tanks leads to a significantly lower gravimetric energy density of the entire system.[1-2] Furthermore, there are many concerns regarding the safety of using hydrogen in different applications because of its inherent flammable characteristics especially in higher concentrations. Liquid hydrogen has frequently made headlines for its potential dangers and as it is odorless and colorless, any leak detection poses a severe challenge. To overcome these obstacles, hydrogen-rich liquid organic molecules have been considered for the generation of hydrogen on demand.[3-4] In particular, C_1 molecules as reasonable alternatives to conventional fossil fuels have been widely discussed as attractive renewable hydrogen carriers.[3-5] However, not all C_1 molecules are equally attractive because on the one hand, the activation of hydrogen-rich methane (25 wt-% H_2) is very challenging and energy intensive; while on the other hand, formic acid provides a comparably low energy content (4.4 wt.-% H_2). Therefore, methanol is currently considered as the most promising C_1 unit owing to its high hydrogen content (12.5 wt-%) and its rather facile activation compared to methane. In addition, methanol exists in the liquid form at ambient conditions which makes its applications even more attractive for its conversion to hydrogen and carbon dioxide. These characteristics have caused major attraction from the scientific community over the past decade in order to establish a carbon-neutral methanol economy.[1,4] However, one of the main sources of methanol synthesis is still fossil fuels which causes its application in hydrogen production to be not in accordance with green and sustainable chemistry principles. Therefore, the methods described herein will be of interest when methanol is produced from renewable sources and especially CO_2 (Olah Plant). In this way, the problem with CO_2 production during the process would be overcome as the whole protocol would be CO_2-neutral. Another main drawback for low-temperature reforming of methanol is the initial endergonic step to convert methanol to formaldehyde which causes the entire methanol reforming process to be net energy-consuming.[1,4] So far, even in presence of the most effective catalytic systems, this activation barrier can just be overcome by providing the additional energy through thermal heating of the methanolic media. In stark contrast, the decomposition of formaldehyde hydrate (methanediol; 8.4 wt.-% H_2), another alternative C_1 molecule, follows an exergonic decomposition pathway producing solely hydrogen and carbon dioxide.[1,4] Formaldehyde is a naturally occurring compound which is for example emitted by vegetation and converted by living species.[1, 5-7] It also has a crucial role in the formation of amino acids, carbohydrates (via formose reaction in the Calvin cycle) and other organic molecules, and therefore formaldehyde plays certainly a critical role in the origin of life on the earth and the universe.[2, 8-9] Moreover, this compound is not only produced naturally from the biodegradation of organic matter or enzymatically through C_1-molecule oxidation or dehydrogenation, but also is industrially produced through high-temperature methanol oxidation and used in many industrial processes for the production of modern daily life commodities (inks, resins, dyes, etc.).[1, 2, 4, 5, 10]

Contrary to the high-temperature industrial processes, bacterial methanol and formaldehyde metabolisms take place under ambient conditions at low-temperature,[2, 6, 11-13] where the oxidation of methanol to formaldehyde remains the most energy intensive step while further oxidation of formaldehyde to formate and carbon dioxide are less energy intensive. The methanol conversion can take place with oxidase or dehydrogenase enzymes respectively mimics, and these reactions can be performed coupled and decoupled to NAD^+/NADH for the

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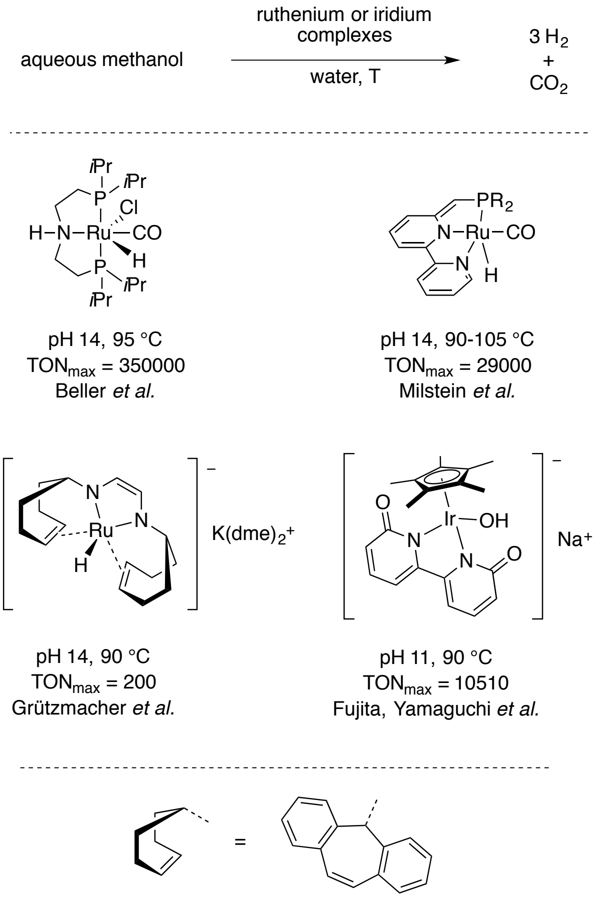
generation of hydrogen.[4] Thus, considering the role of formaldehyde in natural energy conversion processes, there is no doubt that this C_1-molecule represents another promising energy carrier at least for low-temperature energy conversion processes.

In this concept article, we provide a brief overview from a personal perspective of the recent achievements towards bio-inspired low-temperature methanol and formaldehyde reforming. We hope this concept article will inspire the research field to combine synthetic and biological chemistry towards solutions for low-temperature energy storage and energy conversion based on renewable C_1-molecules.

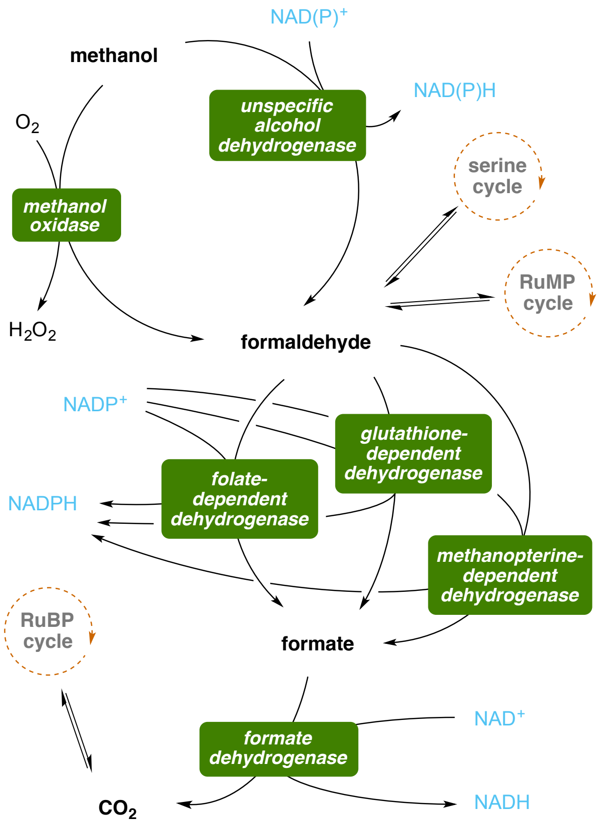
Methanol dehydrogenation – in homogeneous catalysis and in Nature

Owing to the unfavourable initial activation barrier of the methanol-to-CO_2 conversion, methanol reforming was for a long time limited to high temperature heterogeneous approaches. In recent years, however, a number of successful examples of utilizing defined transition metal complexes for hydrogen production from aqueous methanol found their way into the literature. All catalytic systems share some basic features such as reaction temperatures close to 100 °C and the use of basic additives. Particularly, the high pH appears to be a crucial prerequisite as it substantially increases the boiling point of the aqueous methanol solutions as well as enabling formation of more reactive alcoholate species. On the flip side, depending on the actual catalyst, these alkaline additives reduce the efficacy of the system to a certain extent by lowering the effective energy content. A good example for this issue can be seen in the protocol introduced by Beller *et al.* Here, ruthenium complexes, allow an efficient ambient pressure, low temperature aqueous-phase methanol dehydrogenation process, however, the best results are obtained only under strongly basic conditions (8 M KOH). A second common denominator in all homogeneous systems is the cooperative ligand architecture. Both the ruthenium pincer complexes by Beller and Milstein, respectively, as well as Grützmacher's tetradentate olefin/*N,N* structures[14-16] thus allow the intermediate of storage of hydrogen by shuttling of proton and hydride equivalents derived from methanol via the metal core and ligand-backbone to subsequently yield H_2 through proton-hydride recombination. In addition to the effective ruthenium-catalyzed procedures, Fujita, Yamaguchi *et al.* contributed with an iridium-based alternative to the methanol reforming catalyst family. While the bis-pyridonate portion as part of a piano stool arrangement maintains the cooperative ligand character of all methanol-active systems, the Fujita-Yamaguchi approach distinguishes itself by its independence from superstoichiometric basic additives. In presence of only 0.5 mol% NaOH, the iridium complex exhibits good activity and is capable to generate hydrogen efficiently under significantly less alkaline conditions. The higher cost of the central metal is thus more than compensated by the advantage of a milder reaction environment, which represents a crucial direction for future developments in the field.



Scheme 1. Transition metal-catalysed homogeneous methanol reforming.

Methanol activation is not limited to the field of transition metal catalysis but is likewise found in Nature in various shapes and forms. Enzymatic degradation of methanol as part of the general catabolism is widespread across species as for example performed in a nonspecific manner by cytochromes or the catalase-H_2O_2 system.[4] The C_1 carbon pool, however, can also be utilized as a distinct source of energy and/or carbon building blocks. Here, microbial methylotrophic organisms exploit highly effective biocatalytic systems to harvest the reduction potential of methanol (and its oxidized derivatives) for the generation of reduced nicotinamides as biological equivalent to dihydrogen or other chemical reducing agents (Scheme 2). In addition, formaldehyde, as well as the terminal oxidation product carbon dioxide, are taking important roles in the microbial metabolism as building blocks in the pentose phosphate cycles (RuMP and RuBP) and the serine cycle in bacteria,[17] or the xylulose monophosphate pathway in methylotrophic eukaryotes[18] En route to carbon dioxide, various pathways for the room temperature activation of C_1 molecules are found starting with the dehydrogenation of methanol. The natural formation of formaldehyde hydrate from methanol is hence catalysed by either oxidases or dehydrogenases through transfer of the first reducing equivalent to dioxygen or an oxidized nicotinamide cofactor, respectively.[2,4] Mediators for the formaldehyde oxidation include a series of different dehydrogenases that promote further dehydrogenation to formate, or formic acid derivatives which are subsequently hydrolyzed, depending on the required small molecule cofactor involved in the process (such as glutathione, tetrahydrofolate or methanopterine).[4] As for the alcohol dehydrogenase, also the second reduction equivalent can be stored in form of NADPH. In the final step, formate is converted to CO_2 by means of another specific dehydrogenase in order to harvest the third hydrogen equivalent and to complete the full oxidation pathway of methanol.[4]



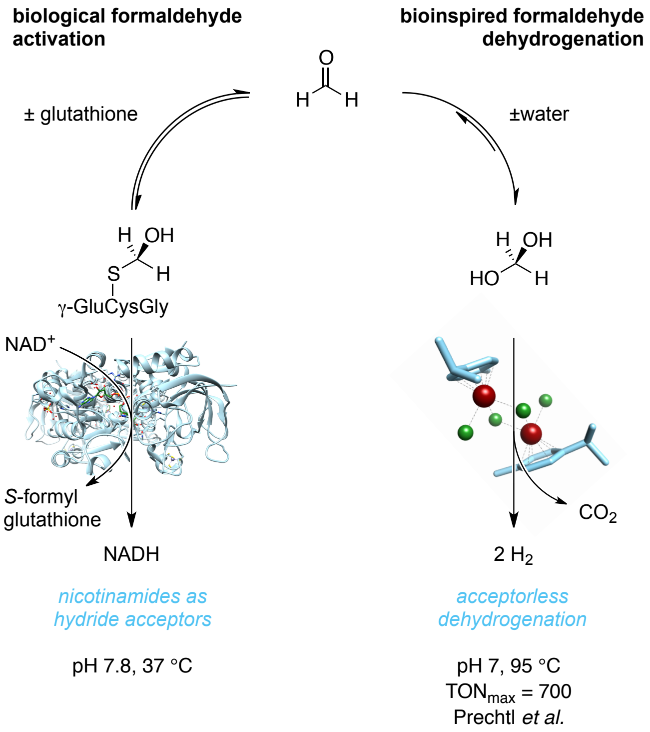
Scheme 2. C1 metabolism as part of the biosynthetic network in methylotrophic microorganisms.

Nature is thus providing us with an elegant blueprint in how to employ methanol as promising liquid organic hydrogen carrier (LOHC) on the basis of ingenious cofactor-enzyme couples and effective catalytic cascades. Moreover, the biological tools of the C_1 metabolism might be suitable for the design of chemoenzymatic cascades where, though not entirely trivial (vide infra), parts of the natural pathway are interconnected with metal-based catalytic entities to gather access to novel low temperature hydrogen-liberating systems.

Organometallic catalysts for formaldehyde activation

Among the potential organic intermediates en route to carbon dioxide only formaldehyde, or rather the hydrated form methanediol, qualifies as suitable substrate for chemoenzymatic processes that would combine biological methanol activation with metal-mediated acceptorless dehydrogenation. Enzymatic pre-activation of methanol to formalin results in an acceptable remaining hydrogen weight efficiency of 8.4%, while formate as the next intermediate in line already substantially lost its liquid organic hydrogen carrier properties (4.4 wt% H_2). Hence, transition metal species that combine activity in the decomposition of formalin to dihydrogen with a high tolerance for an aqueous, non-inert environment and the presence of polar biomolecules pose one crucial prerequisite for any attempt in bio-metal-coupled approaches of this kind.

In 2014, our group reported on the first successful system to perform formalin reforming utilizing homogeneous catalysts. The methodology mimics the natural blueprint by nucleophilic preactivation of formaldehyde, where water is taking the role of glutathione to generate a tetrahedral intermediate that can be readily dehydrogenated. The commercial, dimeric complex $[(Ru(p\text{-cymene}))_2(\mu\text{-Cl})_2Cl_2]$ has been identified as the ideal precatalyst for this transformation.[3] It has been proven that aqueous formaldehyde, or likewise a combination of paraformaldehyde and water, can be effectively employed in the catalytic hydrogen production. The reported bioinspired one-pot process which contains two dehydrogenation steps with very good stability and selectivity to atmospheric oxygen, provides pure H_2 and CO_2 in very good yields (Scheme 3). We also did a detailed mechanistic investigation to obtain a better insight to the mechanism of the reaction. Accordingly, methanediol is oxidized to formic acid while releasing a H_2 molecule in the first step of this reaction. Conversion of formic acid in the next step to carbon dioxide provides another mole of hydrogen. In contrast to most of the reports on dehydrogenation of methanol or formic acid which required basic conditions, this reaction smoothly proceeds at neutral pH. Activation of the hydrogen-rich small molecule generally proceeds at temperatures as low as 25 °C; however, best results and significant turnover numbers required heating to 95 °C. Experiments with ^{13}C-labeled paraformaldehyde and ^{18}O-water confirmed that neither CO nor gaseous formaldehyde have been formed during the reaction which guarantees high efficiency in fuel-cell applications. The results also showed that both (para)formaldehyde and water act as the source of hydrogen.

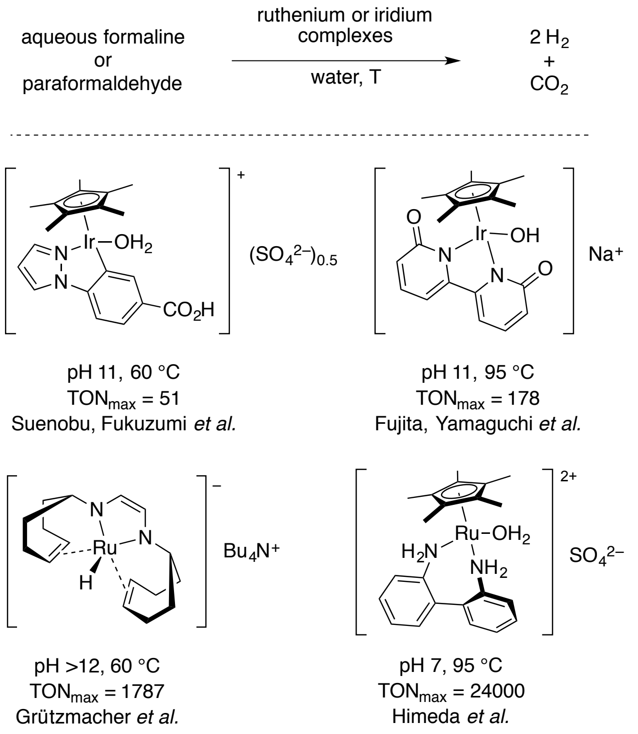


Scheme 3. Bioinspired formalin reforming through nucleophilic preactivation of HCHO.

Already as a stand-alone process, the reported bioinspired nucleophile-induced formaldehyde reforming has many advantages over its complementary methanol reforming process which make it more interesting for hydrogen production. Some characteristics such as long-term stability, non-flammability and recyclability as well as the high hydrogen weight efficiency of methanediol have rendered it a potential compound for mobile applications. The H_2 produced from this process can be used also efficiently for fuel cells as the produced oxygen – the byproduct of water splitting reaction – is used simultaneously for CO_2 formation. The absence of free O_2 has also another advantages: deactivation/oxidation of the fuel cell catalyst as well as explosive oxyhydrogen mixtures are avoided. Overall, compared to the methanol system, the system is here safer as the H_2 is produced in a non-flammable liquid.[5]

Following our original report on the application of paraformaldehyde as a convenient solid hydrogen carrier, other research groups joined in the further development of this promising field of research (Scheme 4). In 2015, Suenobu, Fukuzumi *et. al.* introduced a water-soluble Cp* iridacycle to perform the dehydrogenative decomposition of paraformaldehyde to hydrogen and carbon dioxide in aqueous, slightly alkaline media (Scheme 4).[19] As for the ruthenium-based methodology, theoretically reforming is taking place at ambient temperature, yet, the system showed strong dependence on temperature and acidity and even at 60 °C and pH 11, only moderate turnover numbers were achieved. In the same year, Fujita and Yamaguchi demonstrated the formaldehyde dehydrogenation by means of an alternative, anionic iridium complex carrying a cooperative ligand site.[20] The previously introduced methanol-active iridium bipyridonate naturally also exhibited activity in the H_2-liberating decomposition of formalin reaching moderate TONs of up to 178 upon heating under slightly basic conditions. Another methanol-active catalyst, the dibenzotropyl-based ruthenium complex by Grützmacher, was evaluated against aqueous formalin as hydrogen donor and proved effective as mediator in the hydrogen evolution from this C1 donor.[16, 21] Similarly as to the iridium-based systems, also the Grützmacher catalyst requires rather basic reaction conditions, yet reaches good TONs of close to 1800 at moderate heating to 60 °C. Both, in Fujita's and Yamaguchi's as well as Grützmacher's approaches, the metal centre is coordinated by a chemically and electronically non-innocent cooperative ligand. This non-innocent coordination environment helps the metal centres to readily change their oxidation state. More recently, de Bruin and co-workers have revealed the mechanism of aqueous methanol dehydrogenation based on DFT calculations.[22] Their mechanism which has substantially lower barriers goes through the metal-ligand cooperativity involving the diazadiene ligand. Activation of alcohol is done actively using dad (?) moiety of the ligand. The same group in another report has indicated the effect of solvent molecules in ruthenium-catalysed hydrogen production from methanol.[23] This report reveals the importance of solvent molecules – compared to the gases phase – in affecting the reaction barriers.

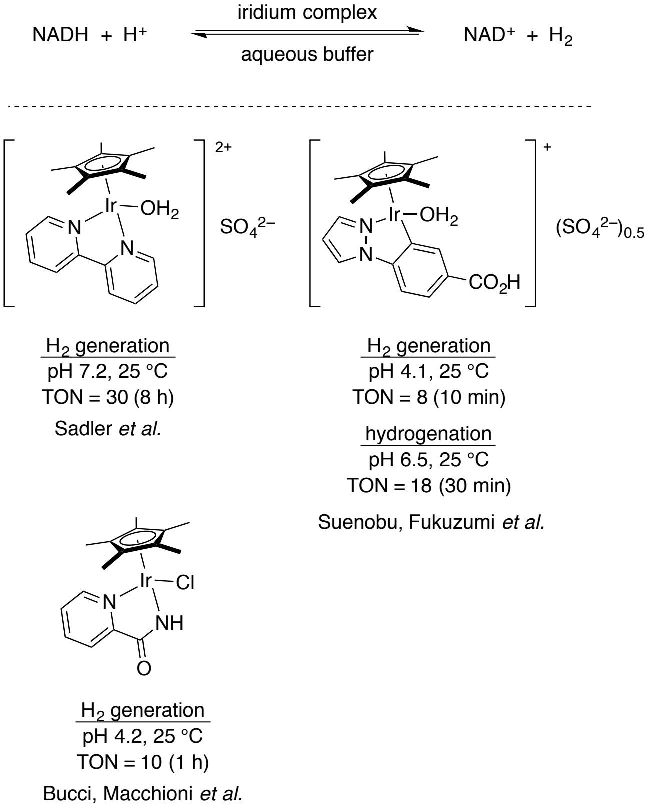
Most recently in 2018, Himeda and co-workers reported on the so far most productive system for the direct reforming of formaldehyde to hydrogen and carbon dioxide.[24] Utilizing a ruthenium-centred piano stool complex decorated by a bidentate 2,2'-dianiline ligand, excellent turnover numbers of up to 24000 were obtained at 95 °C under neutral reaction conditions. Here, the anilino backbone was described as the key feature for the observed high activity as it facilitates the dehydrogenation of methanediol through hydrogen bonding of the NH-moieties.



Scheme 4. Transition metal-catalyzed formaldehyde reforming.

Metal-mediated H_2 production through cofactor dehydrogenation

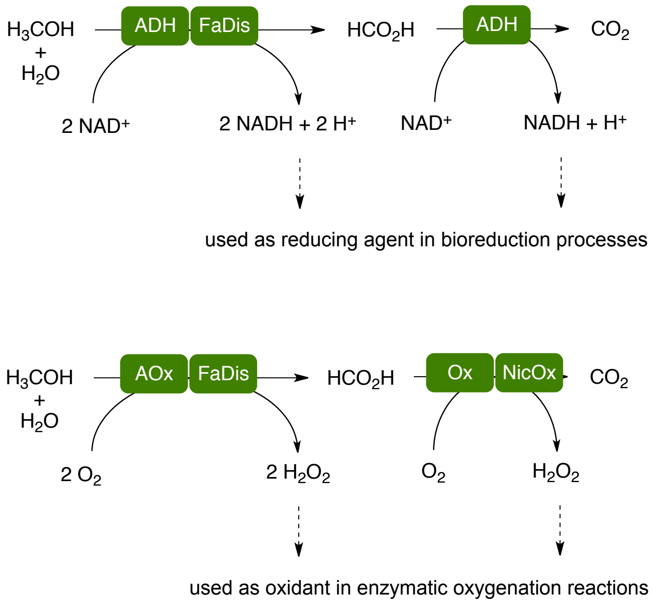
There has been a long-standing interest in redox-coupled systems based on the interaction between organometallic complexes and nicotinamides as one of the prototypical biological redox mediators. Particularly the use of Cp* transition metal complexes has been in the focus of multiple studies in order to enable the cofactor regeneration in reductive biocatalytic transformations without the need for complex enzyme-based recycling systems. Initially targeting metal-enzyme-coupled transfer hydrogenations, both chemical (e.g. through formate) and electrochemical methods have been reported to fuel NADH-consuming biotransformations on basis of rhodium piano stool complexes.[25] Likewise, NAD^+ regeneration was achieved through iridium- and ruthenium-mediated reduction of quinones or pyruvate as sacrificial agents.[26-27] The transfer hydrogenation was further exploited in vivo with iridium complexes acting as reduction catalysts for the removal of xenobiotic aldehydes from mammalian cell lines using NADH as terminal reductant.[28-29] Additionally, an oxidase-like activity of iridium metallacycles was discovered where NADH is driving the generation of hydrogen peroxide from dioxygen.[30] The metal-catalyzed interaction between dihydrogen and nicotinamides, however, remained challenging and only recently the first effective systems appeared in literature (Scheme 5). Sharing the iridium half-sandwich motif as common feature, the groups of Sadler[27] and Fukuzumi,[31] as well as Bucci and Macchioni[32] reported individually of systems capable of performing the acceptorless dehydrogenations of reduced nicotinamides. In addition to superior turnover frequencies, Fukuzumi's pyrazole-based iridacycle showed high reversibility in this process and could hence be employed both for the hydrogen production from NADH as well as for the regeneration of NADH under hydrogen atmosphere. Although some examples include hydrogen production capabilities in close to neutral conditions, the pH of the solutions played a major role in all systems, and both reactions, the hydrogen evolution and the hydrogenation, showed higher activity at lower pH. While worth a note in typical organometallic setting, pH optima below 5 need to be considered a severe limitation in chemoenzymatic scenarios. Thus, in the context of cofactor-coupled hydrogen production further developments regarding nicotinamide-driven acceptorless dehydrogenation seem crucial.



Scheme 5. Iridium-catalysed acceptorless dehydrogenation of reduced nicotinamides.

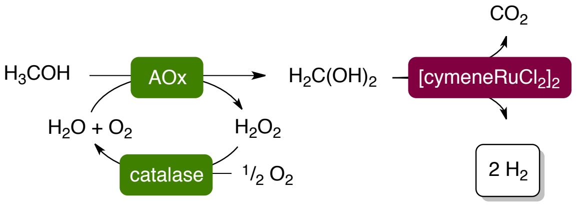
Chemoenzymatic Methanol Reforming Networks

Chemoenzymatic coupling of a biocatalytic activation of methanol and the extraction of hydride equivalents to form dihydrogen can proceed in various ways, depending on the nature of the initial activation, as well as depending on the way how to couple the individual processes. Though many different enzymatic pathways could be generally exploited, practical synthetic applications of methanol-driven processes are rather rare. In 2015 the group of Hollmann reported on a fully biocatalytic sequence combining a methanol-activating nicotinamide-dependent biocatalytic couple, an alcohol dehydrogenase (ADH) and a formaldehyde dismutase (FaDis), with a formic acid-oxidizing dehydrogenase (FDH) (Scheme 6 top).[31] Here, the introduction of the dismutase enables the effective extraction of two reducing equivalents from methanol by in-situ disproportionation of the formaldehyde intermediate. In concert with formate dehydrogenase, methanol oxidation can be performed all the way to carbon dioxide by simultaneously generating three equivalents of NADH to be used in reductive enzymatic processes, or potentially also in H_2-liberating chemoenzymatic approaches. The same group also disclosed an alternative system where the reduction potential of methanol as high-density LOHC was utilized in aerobic biocatalytic oxygenation reactions exploiting alcohol oxidases as methanol-active catalysts (Scheme 6 bottom).[32]



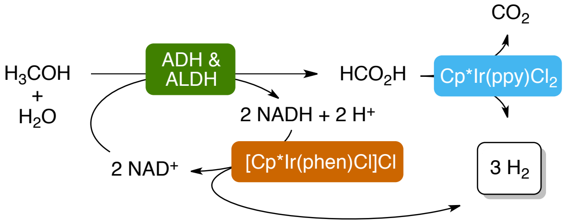
Scheme 6. Complete oxidation of methanol using alcohol dehydrogenase (ADH), formaldehyde dismutase (FDM) and formate dehydrogenase (FDH) to regenerate three equivalents of the reduced nicotinamide cofactor (NADH).

The latter design – taking advantage of the energetically favoured aerobic methanol activation through alcohol oxidases at room temperature – was subsequently used in a first chemoenzymatic approach to generate hydrogen gas directly from methanol without the requirement of extensive heating and/or substantial amounts of base (Scheme 7).[2] Combining an oxidase *C. boidinii* with a catalase to remove the oxidase-derived side product hydrogen peroxide, the metal-enzyme cascade commences with the formal oxygenation of methanol to methanediol. In this C_1 intermediate-coupled system, the previously discovered formaldehyde-reforming cymene-ruthenium catalyst acts as hydrogen producing mediator and converts the formalin to carbon dioxide and two equivalents of hydrogen gas.



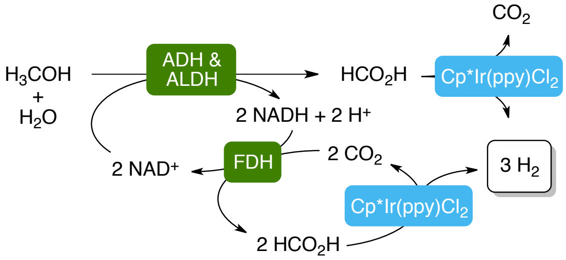
Scheme 7. Alcohol oxidase-driven chemoenzymatic methanol reforming.

The group of Zhou recently disclosed an alternative approach in which a combination of cofactor coupling and intermediate coupling was utilized (Scheme 8).[35] In their initial report, aqueous methanol was biocatalytically dehydrogenated by means of nicotinamide-dependent alcohol and formaldehyde dehydrogenases (ADH and ALDH), respectively, yielding two equivalents of NADH along with one equivalent of formate. The Cp* iridium phenanthroline system that was previously identified by Sadler et al. as effective nicotinamide-oxidizing catalyst was used to recycle the NADH back to NAD^+ while simultaneously evolving two equivalents of H_2. At the same time, formate was dehydrogenated by a polymeric iridium complex based on a polypyrrol backbone converting the remaining C_1 intermediate to CO_2 and another hydrogen molecule. Although this bifurcation pathway and its necessity to engage two distinct organometallic species may be considered less elegant, it represents the very first example to effectively generate three moles of H_2 gas from aqueous methanol.



Scheme 8. Formate-coupled complete dehydrogenation of aqueous methanol.

Shortly after their original report, Zhou and co-workers presented a next-generation design making the second metal-based mediator obsolete (Scheme 9).[36] By supplementing the two existing C_1 dehydrogenases with an additional formate dehydrogenase (FDH), the latter one engages in the recycling of NAD^+ by reductive conversion of catalytic CO_2 to formic acid. Though maintaining a bifurcated pathway, this design results in an effective intermediate-coupled system where the final H_2 liberation occurs solely through the well-established decomposition of formate through the polypyrrol-bound iridium. Thus, also this chemoenzymatic cascade – consisting of three enzymes and one metal catalyst – provides high efficiency at low temperatures and enables the production of three moles of dihydrogen per mole of aqueous methanol.



Scheme 9. Triple dehydrogenase system for the chemoenzymatic methanol reforming at room temperature.

Conclusions

In this concept article, we give the reader a short glimpse to recent developments on enzymatic inspired hydrogen production from formaldehyde or methanol in the aqueous media. In particular, C1 molecules as reasonable alternatives to conventional fossil fuels have been widely discussed as attractive renewable hydrogen carriers in recent years. Formaldehyde as a naturally occurring compound which has a crucial role in the formation of amino acids, carbohydrates and other organic molecules, is a potential C1 molecule for hydrogen production. Basically, the decomposition of formaldehyde hydrate (8.4 wt.-% H_2), in contrast to methanol-based reforming processes, follows an exergonic decomposition pathway producing solely hydrogen and carbon dioxide. On the other hand, since many years, scientists have discovered that the answer of many questions can be found in the nature. Accordingly, there are several approaches to improve the hydrogen production from methanol or formaldehyde sources using ingenious cofactor-enzyme couples and effective catalytic cascades. Moreover, the biological tools of the C1 metabolism might be suitable for the design of chemoenzymatic cascades where, though not entirely trivial (vide infra), parts of the natural pathway are interconnected with metal-based catalytic entities to gather access to novel low temperature hydrogen-liberating systems. Actually, formaldehyde and its hydrated form qualify as suitable substrate for chemoenzymatic processes that would combine biological methanol activation with metal-mediated acceptorless dehydrogenation. In this context, different transition metal-based catalytic systems have been demonstrated in absence and presence of co-factors and/or enzymes. Moreover purely enzymatic systems have been applied for the methanol to carbon dioxide conversion. Accordingly, it can be concluded that the structure of the catalysts –and more specifically, the ligand design-and pH of the reaction media are the two main factors which have a key role in engineering of bio-inspired formaldehyde and/ or methanediol decomposition. Other factors such as temperature are of lower but still high importance.

We hope this concept article will inspire the research field to combine synthetic and biological chemistry towards solutions for low-temperature energy storage and energy conversion based on renewable C1-molecules. The future of bio-inspired transition metal-catalysed transformations is not restricted to these findings and there are many other possibilities in the field to be found. The activities in this interesting research field are steadily increasing and it becomes more and more exciting to confront all the future challenges in the area.

Acknowledgements

We gratefully acknowledge financial support provided by the Ministerium für Innovation, Wissenschaft und Forschung (NRW-returnee award 2009), the Heisenberg-Program (Deutsche Forschungsgemeinschaft), the COST Action *"C-H Activation in Organic Synthesis (CHAOS)"*, the Ernst-Haage-Prize 2014 of the Max-Planck Institute for Chemical Energy Conversion and the Academy of Finland (JD & JN, grant No 309990). DAAD and the Academy of Finland are acknowledged for a binational grant. J. E. A. acknowledges the Fulbright Foundation for a scholarship. G. T. acknowledges the Alexander-von-Humboldt Foundation for a fellowship.

Keywords: dehydrogenase 1 • oxidase 2 • formaldehyde 3 • methanol 4 • hydrogen production 5 carbon dioxide

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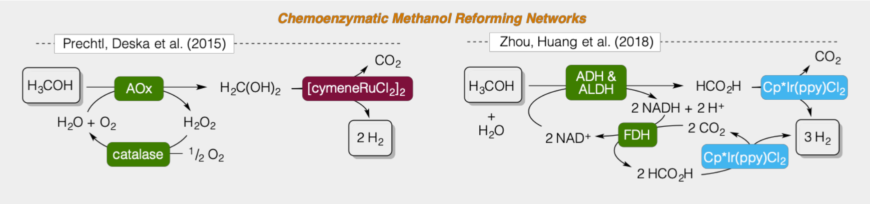
CONCEPT



Conceptual bio-inspired low-temperature energy conversion processes may lead one day to more efficient energy storage systems enabling hydrogen generation for hydrogen fuel cells at ambient conditions using C1 molecules as fuels.

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Page No. – Page No.

Chemoenzymatic Hydrogen Production from Methanol Through the Interplay of Metal Complexes and Biocatalysts