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Viewpoint on the Partial Oxidation of Methane to Methanol Using Cu- and Fe-Exchanged Zeolites

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Abundant and inexpensive reserves of CH_4, obtained from increased production of natural gas, can effortlessly be incorporated into the current petrochemical infrastructure via the conversion to methanol, which is a staple of the petrochemical industry. Although oxidative C−H bond activation of CH_4 is thermodynamically and kinetically accessible at low temperatures, few catalysts are capable of preventing overoxidation of methane to carbon dioxide. This lack in selectivity arises from the high C−H bond energy (415 kJ mol^{-1}) of the methane molecule in comparison to the lower C−H bond energy of the partially oxidized products, which results in further oxidation through consecutive reactions. Currently, the catalytic production of methanol from methane, accomplished through the two-step process of high temperature (~1170 K) steam reforming to syngas and its subsequent conversion over Cu-based methanol synthesis catalysts, is effective only at large scale. To date, no synthetic catalyst exists that can convert methane to methanol in high yields using oxygen as the sole oxidant in a single step.

Conversely, biologically derived methane monooxygenase proteins (MMOs) transform methane and oxygen into methanol with remarkable selectivity[1,2] under ambient conditions through the use of NADH as a reducing agent for the activation of oxygen before the partial oxidation of methane on iron (soluble MMO) or copper active centers (particulate MMO).[1] Accordingly, most direct partial methane oxidation schemes using synthetic catalysts have focused on the formation and reactivity of Fe- and Cu-oxygen species akin to those found in biological systems. The proper ligand field environment afforded by Fe and Cu ions generates electrophilic metal−oxygen species capable of attacking the strong C−H bonds of CH_4. The most promising C−H activation catalyst candidates thus far are Fe- and Cu-based zeolites, where $Fe^{IV}{=}O$ and $Cu^{III}{-}O{-}Cu^{III}$ are believed to be key active site motifs for the selective oxidation of CH_4 to CH_3OH.[3,4] Until recently, it was believed that these sites could only operate stoichiometrically,[5−8] but Román-Leshkov and co-workers demonstrated the existence of sites operating catalytically at steady state for partial methane oxidation using O_2 as the sole oxidant in a variety of Cu-exchanged zeolites.[9] Despite the tremendous potential of these materials, high methanol selectivities could only be achieved at low conversions (<0.1%). Indeed, theoretical studies predict that overoxidation of CH_3OH into CO_2 and H_2O at isolated Cu^{2+} sites will proceed extensively at CH_4 conversions above 0.2%.[10] To circumvent this predicted limit on conversion, the protection of methanol by the formation of more stable products that are more resistant to subsequent oxidation has been discussed by Ahlquist et al.[11] and more recently by Ravi et al.,[12] and these concepts will be emphasized herein. Notable implementations are the Shilov system,[13] which produces chloromethane from methane, and the Periana system,[14] which activates methane to methyl bisulfate. While zeolite-based technologies circumvent the experimental pitfalls of multi-reactor, high-pressure, and high-temperature systems, numerous challenges remain in obtaining high methanol yields and inhibiting excess oxidation.

We are still far from developing an industrially viable catalyst for this transformation, at least in part because nature uses a combination of effects that are difficult to replicate in artificial systems. Specifically, MMOs possess two key features that result in selective methanol production: (1) ligand fields that induce high-spin electronic configurations at the transition-metal sites, which induce highly reactive oxidative and reductive environments and (2) a complex gating mechanism that influences the lability and dynamic binding of reagents to the active site, which enables methanol transport out of the active site pocket while also forbidding back diffusion.[15] In this Viewpoint, we analyze both aspects of the enzymatic system in the context of replicating them in synthetic catalysts. We begin by describing how zeolites share many of the same attributes in terms of site isolation and ligand field strength with metalloenzymes, and we briefly discuss the main achievements in this area. Next, we present an overview of our current understanding regarding the transport mechanism in MMOs for protecting methanol from further oxidation and enabling 100% selectivity to methanol formation.[1,2] Lastly, we present an outlook on future directions and potential strategies to combine these features in a truly biomimetic synthetic platform. The importance of the concept of product protection in methane activation has been discussed for decades, yet we believe this idea is still overlooked in the pursuit of a biomimetic methane partial oxidation system. We also note that our goal is not to present a comprehensive review of the partial methane oxidation field. Rather, we aim to present a

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viewpoint on the need to engineer synthetic methane oxidation catalysts with properties that extend beyond an active site capable of activating C−H bonds.

In nature, as in artificial systems, the ability to generate reactive oxygen species at metal active sites is critical to selective methane oxidation. In the soluble MMO (sMMO) catalytic cycle, Proshlyakov and co-workers confirmed the previously hypothesized structure of Q as a bis-μ-oxo diiron diamond core structure (Figure 1).[16−20] In sMMO, Q forms from intermediate P, a *cis*-μ-1,2 peroxo-bridged di-iron complex via proton transfer and homolytic cleavage of the O−O bond.[21,22] Formation of P occurs via a two-electron transfer to the two Fe atoms to obtain Fe(II),[23] association of O_2 to an open binding site,[24] and then conversion to a peroxo-species.[25]

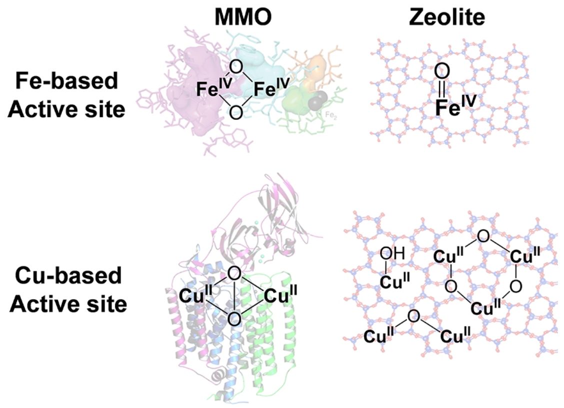

Figure 1. Active site motifs for Fe- and Cu-based enzymes and zeolites.

In an attempt to replicate the Fe sites present in sMMO, Fe-exchanged zeolites have been heavily investigated. Partial methane oxidation in Fe-exchanged zeolites was first observed by Panov and co-workers, who demonstrated methanol can be obtained in a cyclic process.[26−28] Specifically, the Fe active site was first activated by N_2O at high temperatures (∼523 K) to form the α-site, CH_4 was then activated to form CH_3O- and $-OH$ species on these active sites at reduced temperatures, often as low as room temperature, and finally methanol was extracted with water. While water was required to extract methanol, surface-bound methanol was shown to migrate from the α-site and localize on other Bronsted acid sites, allowing for regeneration of the active site in a quasicatalytic process.[29,30] Above 473 K, methanol desorbed spontaneously, resulting in a continuous process.[29] Recently, Snyder et al. identified the active site as a mononuclear, high-spin Fe(IV)═O species using magnetic circular dichroism.[3] These authors highlighted the importance of the zeolite topology, which provides the appropriate geometric constraints around Fe to maintain vacant the *trans* axial position of α-O and produce an entatic state.[3] Activation of Fe with molecular O_2 at mild temperatures has not been demonstrated to date.

In an alternative aqueous synthetic pathway, methanol was produced over Fe-zeolite catalysts using H_2O_2 as an oxidant at low temperature (∼323 K). In a batch system, a maximum conversion of 10.1% and a methanol selectivity of 93% was reported[31] while, in a continuous system, a maximum conversion of 0.5% and a methanol selectivity of 92.2% was reported.[31−33] The catalytic cycle proceeded by the formation of methylhydroperoxide that sequentially decomposed to methanol and then to formic acid.[34] Selectivity was further improved by introducing Cu alongside Fe within the zeolite, which prevented the oxidation of methanol to formic acid.[31] Carbon dioxide accounted for the balance of products. Characterization studies demonstrated that the active site is an extra-framework diiron site that, upon activation with H_2O_2, forms an Fe-OOH intermediate.[35]

The mechanism for the activation of methane is unknown in both sMMO and Fe-based zeolites. Multiple C−H activation mechanisms for sMMO have been proposed, including radical, cationic, and concerted mechanisms. In sMMO, using chiral ethane as a substrate, hydrogen abstraction from methane was suggested to occur via a radical intermediate where the methyl radical rotation is constrained by interaction with the diiron center.[36,37] Although understanding of the genesis of active sites and the reaction mechanism involved in methane oxidation is critical for future catalyst design, the Fe-based zeolite approach is industrially unfeasible because expensive oxidants (in many cases, more valuable than methanol itself) are needed to activate the Fe site. In addition, a gas-phase approach would require a looping process with temperature and feed changes that are challenging to implement industrially. The aqueous route is also limited primarily due to the challenge of recovering dilute methanol from an aqueous solution.[38] Further study of these systems should focus on using abundant and inexpensive oxidants in a continuous system.

While the structures of key Fe intermediates in sMMO have been identified and extensively studied, there is no consensus on the structure of the Cu active site nor its mechanism for methane activation in particulate MMO (pMMO). Some of this lack of knowledge can be attributed to challenges with enzyme purification. Mononuclear, binuclear, and trinuclear copper complexes have all been proposed. Most recently, Rosenzweig and co-workers displayed evidence for a binuclear copper core through the use of kinetic and EXAFS experiments.[39] Based on density functional theory (DFT) and quantum mechanical/molecular mechanics (QM/MM) calculations, both mononuclear and dinuclear Cu centers are capable of oxidizing methane. However, both active site motifs exhibit shortcomings: mononuclear Cu was modeled as a nonconserved site[40] and the proposed mechanism involving a dinuclear Cu site proceeds via Cu(III),[40,41] which has not been observed experimentally.[42] The proposed dinuclear oxygen activation mechanism necessitates O_2 insertion to form a $\mu-\eta^2$: η^2-peroxo-Cu_2(II) site that is then converted to a C−H activating catalyst site (either a di(μ-oxo)Cu(II)Cu(III) or di(μ-oxo)(μ-hydroxo)Cu(II)Cu(III) species). Limited reports evince a $\mu-\eta^2$: η^2-peroxo-Cu_2(II) species but this species was not observed upon incubation of pMMO with a saturated oxygen buffer.[40,41] Limited mechanistic studies have been performed with pMMO. Activation of chiral ethane in pMMO was suggested to occur via a concerted pentacoordinate C−Cu or C−O intermediate before insertion of oxygen and cleavage of the C−H bond.[43] However, a radical or cationic mechanism cannot be ruled out if pMMO slows the rate of C−C bond rotation similar to sMMO.[44]

Cu-exchanged zeolites have also been thoroughly studied in an attempt to replicate the copper activity of pMMO. The catalytic conversion of methane to methanol over Cu-exchanged zeolites is enabled by the oxidizing capability of Cu-based catalysts. Cu has been used to catalyze a plethora of oxidation chemistries[45] and copper oxides are known to promote CH_4 combustion.[46] Process conditions, zeolite composition and structure, and Cu speciation must be optimized in order to singly oxidize CH_4 and avoid complete combustion to CO_2. Catalytic conversion of CH_4 to CH_3OH can be accomplished by using H_2O_2[32] or N_2O[6] as an oxidant. Methane oxidation via aqueous H_2O_2 has been reported to result in high CH_3OH selectivity; Kalamaras et al.[47] reported ~75% selectivity to CH_3OH in the presence of 0.5 M H_2O_2 over a Cu/ZSM-5 catalyst. Samples catalyzed multiple turnovers as evidenced by a MeOH/Cu molar ratio >4 for a 2.6 wt % Cu/ZSM-5 catalyst, demonstrating that active sites are completing multiple catalytic cycles and selectively synthesizing CH_3OH beyond a stoichiometric amount while in the presence of excess oxidant.

For Cu-zeolites, proposed active sites involve monocopper, dicopper, and tricopper species (Kulkarni et al.,[48] Groothaert et al.,[6] and Grundner et al.,[7] respectively). Results from DFT-based investigation of methane activation support the homolytic cleavage of C−H bonds by radical-like oxygen atoms to form a radical methyl intermediate that is subsequently re-bound to the hydroxyl species.[4,49] Methanol desorption often presents the largest energetic barrier to complete catalytic turnover and the presence of H_2O is purported to stabilize and facilitate methanol emission.[49] The complexities introduced by varying zeolite topologies, locally confined reactant concentrations, Cu-speciation, and the nature of the oxidant all inhibit overgeneralization of C−H activation mechanisms.[50,51]

When considering the use of O_2 as the oxidant, experimental precautions must be taken in order to minimize extensive oxidation. Cyclic chemical looping procedures have been shown to yield high selectivity to methanol by completely separating the oxidant from CH_4 by using inert gas purges between the O_2 activation step and the introduction of CH_4 over the Cu-zeolite.[12] These looping procedures circumvent overoxidation problems that arise because of the simultaneous presence of large concentrations of O_2 and CH_4. Overoxidation can also be minimized by limiting the amount of O_2 within the reactor. Román-Leshkov and co-workers have reported the steady-state conversion of methane to methanol in the presence of very low concentrations (~100 ppm) of gaseous O_2[9] under a flow of CH_4, H_2O, and O_2. CH_3OH production rates were invariant with O_2 concentration over the ranges studied, demonstrating the thermodynamic favorability of Cu oxidation in the presence of extremely dilute O_2 concentrations. While this method of steady-state production of methanol is appealing, careful consideration must be taken in order to optimize the concentration of O_2 to oxidize and maintain catalytically active sites while minimizing the presence of excess O_2 that results in deleterious complete combustion reactions. More recently, the use of H_2O as the sole oxidant to produce CH_3OH was published by Van Bokhoven and co-workers.[52] The relatively weak oxidative potential of H_2O, relative to O_2, in conjunction with the natural abundance of water, highlights the appeal of conversion processes based on these reactants. Note that the thermodynamics of this system are challenging ($\Delta G_{\text{reaction}} \approx 117$ kJ mol^{-1} at 200 °C[53]). Further study in this direction is definitely warranted.

Undoubtedly, an understanding of both a catalyst's active site structure and its local environment is necessary to continue to engineer improved synthetic catalysts. In this respect, the role of the zeolite must also be optimized in CH_4 oxidation chemistry. Different local confinement effects and the pore sizes present in varying zeolite topologies can offer diverse environments that stabilize species along every step of the reaction pathway. The synthesis of Cu-zeolites also offers the opportunity to incorporate cooperative active sites within the catalyst, most specifically Cu-species and Brønsted acidic protons. Mahyuddin and co-workers[54] correlated the Cu−O−Cu angle to the alteration of the electron acceptor orbital of the $[Cu_2(\mu\text{-}O)]^{2+}$-zeolite species and subsequent decrease in activation energy of rate-determining C−H bond cleavage, and this angle is specifically set by the zeolite topology and the crystallographic location of the active site. Sushkevich and others[52] have correlated the appearance of H^+ and $-OCH_3$ moieties via Fourier transform infrared (FTIR) spectroscopy upon C−H activation, and Kalamaras and others[47] have demonstrated systematically increasing yields of CH_3OH as a function of increasing catalyst Brønsted acidity, implicating the mechanistic relevance of protons in partial methane oxidation chemistry. Synthetic control over the catalytic porous microstructure is a necessary tool to optimize reactant environment and active site densities to allow for tunable control over the reaction energetics; the knowledge to optimize catalyst synthesis procedures is predicated upon a fine understanding of the mechanistic details of C−H activation.

Similar in essence to zeolites, in terms of pore topology and local structure variability, metal−organic frameworks (MOFs) are microporous materials made from inorganic building blocks bridged by organic ligands, defining a plethora of pores of 1−4 nm in diameter that offer virtually unparalleled tunability in the solid state. One of the most striking features of MOFs that remains remarkably unexplored is the unique coordination chemistry of the inorganic building units, which are nodes made from multimetallic clusters. These nodes can be thought of as independent molecules that are pinned to a solid porous matrix and are therefore primed for interaction with small substrates such as O_2 and methane (see Figure 2).

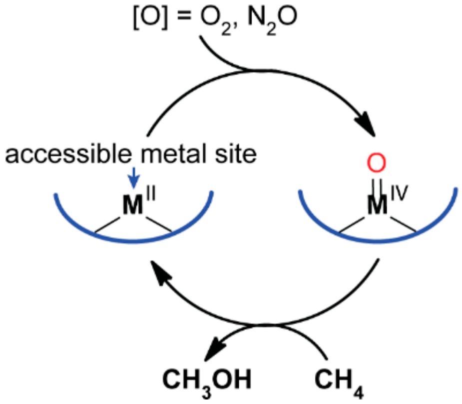

Figure 2. Conceptual activation of CH_4 at a high-spin high-valent metal-oxo species.

MOFs are most commonly composed of common enzyme ligands including carboxylic acids, imidazoles, phenols, or thiols, and the MOF nodes define metal coordination environments with ligand field strengths that also mimic those of metalloenzymes. Reasons for the importance of the relatively weak fields conferred by MOF ligands, in relation to reactivity, are 2-fold: (1) they establish labile bonds with the metal ions, thus offering dynamic, flexible coordination environments that could imitate enzymes and (2) they lead to high-spin electronic configurations, promoting more facile oxidative and reductive chemistries.

As discussed above, a key feature contributing to the exquisite selectivity of enzymatic systems is site isolation. In MMOs, active sites are protected from deleterious reactions by protein scaffolds. This is typically impossible with homogeneous systems as attempts to control access to the active site necessarily result in changes to the chemical nature of the active site, adding further complexity to the tuning of homogeneous systems. Indeed, whereas structural models of virtually any metalloenzyme can be synthesized by judicious ligand design, functional mimicry of the natural systems remains elusive because bimolecular deactivation, aggregation, and ligand denaturation often compete with productive catalysis. Zeolites address the challenges faced by homogeneous systems by protecting the catalytic sites inside rigid pores that can be viewed as mimics of the protein scaffold, albeit using primarily inorganic framework elements, which limits the tenability of their transport properties (vide infra). However, the metal loading in zeolites is often limited and the structure of the active site is often difficult to characterize. MOFs typically exhibit higher active site loadings and coordination environments that are structurally well-defined and more tunable insofar as electronic structure and reactivity are concerned. Recent work by Dincă and co-workers have shown that active metals can be substituted post-synthetically into MOFs.[55−58] Accordingly, Ikuno et al. recently demonstrated that the oxidation of methane to methanol occurs on copper-oxo clusters in NU-1000,[59] while work by Osadchii et al. demonstrated this same chemistry with Fe on MIL-53.[60] We expect that these substituted high-valent metal cations will exhibit high-spin states, rendering them active for both electron acceptance and donation.

The combination of advanced characterization and synthesis techniques with rigorous kinetic studies to identify and isolate the active site(s) responsible for the observed catalytic behavior will be an important area of future research for biomimetic processes. The most promising routes for resolving the true nature of the active site(s) necessitate in situ experimentation and operando techniques such as atom-specific Cu-XAS offer enormous potential for isolating active site precursors and observing changes in oxidation state and local environment of Cu that occur during the catalytic cycle and also as a result of reaction condition alterations. Although the technique does constitute a sample averaging that may include inactive moieties, changes observable under transient conditions will provide valuable information about the active site as the catalyst is transitioned between different phases of the catalytic cycle due to reactor and feed conditions. Thus, while there is a wealth of research that implements XAS analysis of active site oxidation state and local environment via ex situ measurements of transient, stoichiometric systems, the use of operando XAS in steady-state systems should be pursued as a method for monitoring the evolution and maintenance of active centers in metal-exchanged zeolites or MOFs for methane activation catalysis. Understanding the catalytically active site will allow for selective control and synthesis of the proper microenvironment necessary for C−H activation to form CH_3OH, which will also facilitate selective scavenging of reactive intermediates to preserve the high selectivity toward non-CO_2 products (vide infra).

While identification of the active site in MMOs is necessary for a biomimetic approach to synthetic methane oxidation catalysts, understanding the role of the reactive environment to enhance transport of reactants and products within the micropores is an equally (if not a more) important task. A critical, yet commonly neglected topic in the community working on synthetic catalysts for partial methane oxidation is the gating mechanism found in sMMOs that enables their near-perfect selectivity to methanol. Specifically, elegant studies by Lippard and Cho et al. showed that the di-iron active site is situated in a hydrophobic cavity in sMMO hydroxylase (MMOH) and that access to the active site is controlled by the regulatory B component (MMOB) inducing conformation changes within MMOH upon MMOB docking (see Figure 3).[15] The enzymatic active site can be accessed via two separate routes: a hydrophobic passage and a hydrophilic pore. When MMOB is not docked on MMOH, the hydrophobic passage is separated from the active site cavity by a phenylalanine gate and the active site can be accessed via the hydrophilic pore. Upon binding to MMOH, MMOB induces a conformation change in this phenylalanine residue, allowing the diffusion of methane and oxygen within the hydrophobic passage to the active site. Simultaneously, the hydrophilic pore is closed, preventing access of unwanted substrates. Once MMOB dissociates from MMOH, the hydrophobic passage is again gated and the hydrophilic pore opens, allowing for methanol and water egress and proton and electron ingress.[15,61] This gating mechanism thus facilitates the removal of methanol to prevent its complete oxidation. One shortcoming noted by Ross et al. is that this model does not explain the observed first-order dependence on the substrates when zero-order kinetics would be expected by this gating mechanism, although this discrepancy could be accounted for by mass-transfer limitations.[62] Similar hydrophobic and hydrophilic cavities have been identified in pMMO, but the roles of these cavities have not been identified.[44] It is possible that a gating mechanism for substrate access that is similar to that observed in sMMO is at play. Without a gating mechanism, the continued oxidation of methanol is possible;

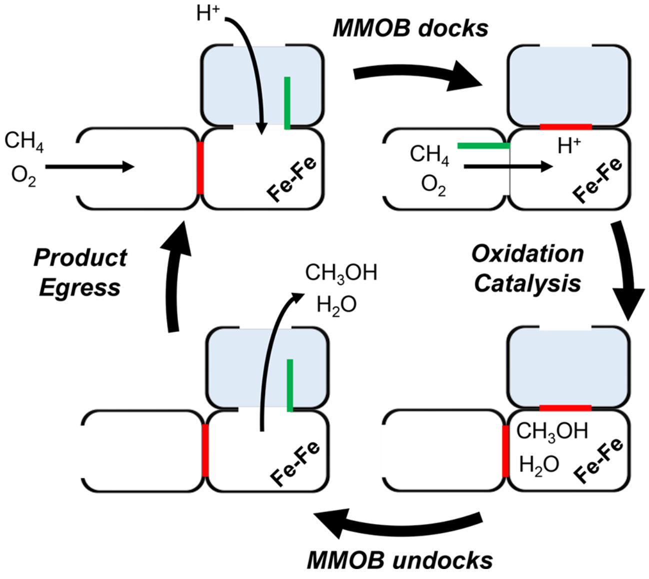

Figure 3. Enzymatic gating process for methane oxidation to methanol.

the interception and removal of methanol from the active site results in the high methanol selectivity observed from sMMO-catalyzed oxidation. To this end, Colby et al. demonstrated that methane monooxygenase of *Methylococcus capsulatus* (Bath) is not substrate-specific and can oxidize methane derivatives, including methanol. In fact, methanol was oxidized three times faster than methane, despite being a product and having a larger Michaelis–Menten constant.[2]

The direct mimicry of this bioenzymatic process, partially enabled by a flexible enzymatic topology, is difficult to accomplish with a zeolitic system because of the comparably rigid zeolite structures. Nonetheless, the shielding of singly activated C–H reaction intermediates can inspire the pursuit of other related capping mechanisms. Shilov et al. demonstrated one of the first instances of this idea using $Pt(II)Cl_2$ in aqueous solution to convert methane to chloromethane, which can react further to obtain methanol.[13] Using Hg and Pt-based catalysts in concentrated sulfuric acid, Periana and co-workers were able to activate methane to form methyl bisulfate, which could be subsequently oxidized to methanol in a sequential hydrolysis step.[14,63] The Periana catalyst was heterogenized by Palkovits et al. by using a covalent triazine-based framework to coordinate with Pt, resulting in a methanol selectivity of >75% in a batch system.[64] More recently, Surendranath and co-workers used $Pd^{II}SO_4$ in concentrated sulfuric acid to produce methyl bisulfate from methane electrochemically.[65] Another route to be explored is the direct sulfonation of methane with sulfur trioxide, which has been demonstrated in liquid methanesulfonic acid[66] and also in fuming sulfuric acid.[67] Methanesulfonic acid can be cracked to produce methanol and sulfur dioxide, which can be reoxidized to sulfur trioxide and then recycled.

Selectivity is an inevitable function of the C–H activation mechanism. A clear distinction must be highlighted between radical-inducing C–H activation mechanisms initiated by homolytic C–H bond cleavage and heterolytic Periana-type systems. The former inherently leads to unselective sequential oxidation events because of the weaker, more-polarized C–H bonds of oxidized products while the latter maintains selectivity to single oxidation events by preferential C–H bond cleavage of the more-reduced substrate as opposed to the more oxidized product.

These heterolytic methods to cleave C–H bonds mimic the enzymatic system by inhibiting methanol oxidation via the formation of reaction products that are less prone to oxidation after initial C–H activation. In a similar vein, the initial C–H activation of CH_4 over Cu-exchanged mordenite leads to the concurrent formation of zeolitic protons and methoxy groups as evinced by FTIR spectra of adsorbed pyridinium ions and $-OCH_3$ groups. These surface methoxy groups can be subsequently removed as gas-phase methanol by H_2O cofeed.[52] The ideal implementation of a selective steady-state process would involve the scavenging of the stable intermediate achieved after C–H activation (i.e., $-OCH_3$ groups) to yield products that are not as susceptible as CH_3OH to overoxidation. In this respect, Román-Leshkov and co-workers showed that Cu-exchanged mordenite zeolites are active for the production of acetic acid from methane via tandem oxidation and carbonylation.[68] This transformation is possible by virtue of a cooperative catalytic effect between redox-active copper sites and carbonylation-active acid sites. Notably, since the acid sites in the 8-member ring side pockets of MOR are the only carbonylation-active sites in the zeolite, acetic acid production from methane in Cu-MOR implies a previously unknown step in the mechanism involving methanol migration from the Cu center to the acid site in the side pocket in similar fashion to the methoxy mobility observed in Fe-based catalysts.[29,30] Industrial implementation of CH_4 activation chemistries could thus potentially lie in the removal of these initially activated C–H species as products that are less susceptible to subsequent oxidation events.

The ideal implementation of a catalytic methane-to-methanol process on an industrial scale necessitates the investigation of multiple primary factors. When considering feasible industrial processes, rates of methanol production should be examined in terms of catalyst quantity and total processing time. Within the chemical looping literature, methanol production is often reported as normalized by catalyst loading, i.e., methanol produced per Cu or methanol per gram of catalyst, yet this reporting ignores relevant downtime during the implementation of cyclic processes. Narsimhan et al. provide the most direct comparison for the rates of methanol production during stoichiometric and catalytic production over a single Cu–H-ZSM-5 at 483 K, reporting a yield of 82 μmol CH_3OH g_{cat}^{-1} during the stoichiometric regime immediately followed by a steady-state production rate of 1.81 μmol CH_3OH g_{cat}^{-1} h^{-1} during the catalytic regime. The looping process involved heating from 483 K to 823 K, a 5 h hold at 623 K, cooling to 823 K, reactor purging with He for 0.5 h, CH_4 flow for 0.5 h, and finally H_2O-aided desorption of methanol that lasted ∼15 h.[9]

A looping process offers the inherent benefits of the separation of the oxidant from methane, aiding in extraction of desirable partially oxidized products and preventing the continued overoxidation of desirable products. However, ignoring heating and cooling times, this entire process consumes >20 h per cycle. Using this time scale to normalize methanol production rates and assuming no deactivation between looping cycles yields a rate of production on the order of ∼4 μmol CH_3OH g_{cat}^{-1} h^{-1}. At first glance, this is twice the rate of production of the catalytic regime. Methodological improvements for increasing the quantity of active sites for C–H activation is dependent upon catalyst formulation, requires further fundamental study, and cannot be simply manually adjusted. Both steady-state and catalytic processes can be further optimized via catalyst synthesis, but there is no evidence to imply the selective benefit of catalyst makeup upon a looping process as opposed to a catalytic process. Upon deeper consideration, one can recognize the inherent limitations of a stoichiometric, cyclic process: the rate of methanol production is fundamentally controlled by the time scale to complete a single looping cycle, and the amount of methanol produced per cycle is limited by the number of active sites within a catalyst. The looping time scale can be modestly adjusted and optimized, but the nature of alternating flows and temperatures remains integral to the cyclic process. If a sufficiently high rate of methanol production can be achieved per cycle, a cyclic process can have industrial application. Conversely, a steady-state system can be manipulated and optimized simply by altering reaction temperature and space velocity to modify rates and selectivity. Using a feasible C–H activation energy of ∼100 kJ mol^{-1} reported by Zhao et al.,[69] steady-state methanol production rates can be doubled simply by a 14 K increase in operating temperature, and this process can run without interruption, barring catalyst deactivation. Unfortunately, a continuous process will always subject methanol to contact with oxygen and subsequent oxidation events, whereas a looping system will innately limit overoxidation because of the separation of these species, resulting in an inherently higher selectivity in comparison to a continuous process. When considering the pros and cons of these separate processes, we believe that the current thrust of technological development should be focused on the exploration and amelioration of steady-state processes.

Two prominent factors in the development of a steady-state methane to methanol process are (1) the oxidant used and (2) the selectivity achieved. As shown in previous work, the use of N_2O and H_2O_2 can provide large conversions and selectivities toward methanol production. Unfortunately, these oxidants are themselves produced in costly industrial processes, minimizing the economic boon from methanol production because of the stoichiometric necessity of costly oxidants. While the use of a reducing agent to facilitate O_2 activation prior to active site generation, much like NADH in MMOs, is attractive, a simple cofeed would not be straightforward as challenges such as the presence of both an oxidant (O_2) and a reductant (e.g., H_2) at elevated temperatures would promote undesirable, unselective reductant combustion. Therefore, the pursuit of an industrial catalytic process should focus on the use of abundant oxidants such as O_2[9] or H_2O.[52]

While a significant amount of study of methane-to-methanol chemistry has focused upon the use of Cu- and Fe-based catalysts, the potential use of other catalyst metals has not been fully explored. Flytzani-Stephanopoulos and co-workers[70] have demonstrated the use of isolated Rh-sites for methane C−H activation, opening up new catalytic avenues for study aside from Cu and Fe.

In conclusion, the stoichiometric conversion of CH_4 and an oxidant urges the use of abundant and inexpensive oxidants such as O_2 or H_2O in pursuit of an industrial process to implement. In addition, methane-to-methanol chemistry is predicated upon the activation of the strong C−H bond of CH_4. The subsequent issues with high selectivity to methanol lie in the relative weakness of the C−H bond strength in the product methanol. Implementation of this chemistry on an industrial scale would theoretically occur in a flow system and yield products resulting from C−H activation but prior to complete oxidation to CO_2. This chemistry is achieved flawlessly via enzymatic gating mechanisms that arrest CH_3OH overoxidation using pliable and coordinating protein structures; identical mimicry of this process is more difficult using more rigid zeolitic structures, but the concept of protecting CH_3OH from overoxidation is vital for the success of methane activation processes. To that end, successful CH_4 activation should be pursued by both designing catalysts with improved activity (e.g., higher active site loadings, tuning of electronic structure and local environment) and by scavenging intermediates resulting from initial C−H activation in order to form stable products that are more resistant to oxidation. For this reason, the "methane-to-methanol" process should be pursued more in terms of simple "methane C−H activation", as opposed to a primary pursuit of CH_3OH when considering the thermodynamic prevalence of complete oxidation of CH_3OH.

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Notes

The authors declare no competing financial interest.

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