Bioinspired Oxidation of Methane in the Confined Spaces of Molecular Cages

Ikbal, S. A.  
Colomban, C.  
Zhang, D. W.  
Delecluse, M.  
Brotin, T.  
Dufaud, V.  
Dutasta, J. P.  
Sorokin, A. B.  
Martinez, A.  

ABSTRACT: Non-heme iron, vanadium, and copper complexes bearing hemicryptophane cavities were evaluated in the oxidation of methane in water by hydrogen peroxide. According to $^1$H nuclear magnetic resonance studies, a hydrophobic hemicryptophane cage accommodates a methane molecule in the proximity of the oxidizing site, leading to an improvement in the efficiency and selectivity for CH$_3$OH and CH$_3$OOH compared to those of the analogous complexes devoid of a hemicryptophane cage. While copper complexes showed low catalytic efficiency, their vanadium and iron counterparts exhibited higher turnover numbers, $\leq$13.2 and $\leq$9.2, respectively, providing target primary oxidation products (CH$_3$OH and CH$_3$OOH) as well as over-oxidation products (HCHO and HCOOH). In the case of caged vanadium complexes, the confinement effect was found to improve either the selectivity for CH$_3$OH and CH$_3$OOH ($\leq$15%) or the catalytic efficiency. The confined space of the hydrophobic pocket of iron-based supramolecular complexes plays a significant role in the improvement of both the selectivity ($\leq$27% for CH$_3$OH and CH$_3$OOH) and the turnover number of methane oxidation. These results indicate that the supramolecular approach is a promising strategy for the development of efficient and selective bioinspired catalysts for the mild oxidation of methane to methanol.

INTRODUCTION

The direct conversion of methane to methanol under mild conditions is one of the major challenges posed to the scientific community because of its crucial industrial and ecological benefits. The selective transformation of CH$_4$ is considered as a particularly difficult task due to the extreme inertness of the methane C–H bond (bond dissociation energy of 104.9 kcal mol$^{-1}$, high pK$_a$, low polarizability, high ionization potential, and negligible electron affinity).$^1$ The current industrial approach to conversion of CH$_4$ to useful products is based on syngas technology demanding large investments and very high temperatures ($>600$ °C). Direct oxidation processes also require high temperatures, but the conversion and selectivity of these processes are still low.$^2$ In contrast, in nature, the aerobic oxidation of CH$_4$ to CH$_3$OH under ambient conditions is efficiently mediated by the soluble (sMMO) and particulate (pMMO) methane monoxygenases found in aerobic methanotrophic bacteria.$^{3,5,6}$ The active sites of these two enzymes are described as non-heme diiron (sMMO) and copper (pMMO) high-valence metal–oxo species, respectively, acting as particularly powerful oxidants.$^7$ In these systems, the active metal center is confined in the hydrophobic cavity provided by the enzymatic architecture. This isolated and constrained hydrophobic environment allows for highly efficient recognition of methane and prevents back-diffusion of CH$_3$OH to the active site, thus preventing its further oxidation.$^8$ This structural organization results in the remarkable efficiency and selectivity of the oxidation of CH$_4$ to CH$_3$OH. There has been an extensive effort to obtain synthetic structural models for the MMO$^9$ however, functional models capable of oxidizing methane are still rare.$^{10}$ Among notable examples of bioinspired catalysts are non-heme copper$^{11}$ and heme diiron complexes,$^{12,13}$ recently described for the mild oxidation of CH$_4$. For instance, $\mu$-nitrido diiron phthalocyanine$^{12}$ and porphyrin$^{13}$ complexes were found to efficiently catalyze the oxidation of CH$_4$ by H$_2$O$_2$ in water at 25–60 °C. However, because the primary methane oxidation products (CH$_3$OH and CH$_2$O) contain more reactive C–H bonds than CH$_4$, their further oxidation occurred, providing
formic acid with a selectivity of 88−97%. Despite the need to prevent over-oxidation of CH₂OH, the implementation of this strategy in biomimetic methane partial oxidation systems is still overlooked. Consequently, to increase the selectivity of methane oxidation for methanol, the structural organization of the active site should be improved. Several approaches to circumventing the higher reactivity of the alkane oxidation products and limiting the over-oxidation reactions have been proposed. The controlled selective oxidations of aliphatic C−H bonds have recently been achieved by supramolecular catalysts either by introducing a recognition group bound to the catalyst (interactions with the substrate such as hydrogen bonding, ligand to metal coordination, or hydrophobic effects) or by building a hydrophobic cavity above the catalytic center. It is in this last category that Cu(II)- and V(V)-based hemi-cryptophanes have been recently described as being highly efficient and selective oxidation catalysts compared to the parent analogues that are devoid of a cavity. Although improvements in reactivity and selectivity of various reactions have been achieved using functionalized molecular nano-reactors, to the best of our knowledge, such a strategy has never been extended to the bioinspired oxidation of methane. The presence of a hydrophobic cavity in the proximity of the catalytic site might result in the preferential binding of CH₄ with respect to the more polar CH₂OH product and favor CH₄ oxidation over over-oxidation reactions. Thus, the more selective oxidation to CH₂OH can be achieved. Therefore, the development of novel artificial models that can simultaneously bind and oxidize methane is highly desirable for exploring the benefits of the supramolecular approach. We present herein a study of the encapsulation and oxidation of methane mediated by vanadium, copper, and iron supramolecular complexes under mild conditions. The interaction between CH₄ and the hydrophobic cavity of hemi-cryptophane was confirmed by a ¹H nuclear magnetic resonance (NMR) study. Six supramolecular complexes, including the two novel tris(2-pyridylmethyl)amine-based hemi-cryptophane complexes Cu(II)(Hm-TPA) and Fe(II)(Hm-TPA) (Scheme 1), displaying various first and second coordination spheres were immobilized onto silica and applied in the heterogeneous oxidation of CH₄ in water by H₂O₂. We demonstrated that changing the nature of the second coordination sphere around the V=O site could lead to improved efficiency or selectivity. Importantly, upon incorporation of a hemi-cryptophane hydrophobic cavity above a non-heme iron unit, both the efficiency and the selectivity for primary oxidation products CH₂OH and CH₂OOH were simultaneously enhanced. This work provides a proof of concept for the potential benefits of developing catalysts bearing a hydrophobic cavity above a bioinspired active center for the direct and clean transformation of CH₄ to methanol.

EXPERIMENTAL SECTION

Preparation and Characterization of Metal Hemi-cryptophane Complexes. To evaluate the importance of the supramolecular structure to catalytic efficiency, several metal complexes bearing a hemi-cryptophane cavity and analogous complexes devoid of the cage were prepared. Complexes Cu(II)(Hm-TREN), V(Hm-TKA), V(Hm-BINOL-TKA), and V(Bz-BINOL-TKA) (Scheme 1) were obtained according to previously reported procedures. In addition, the new complex Cu(II)(Hm-TPA)(ClO₄)₂ based on the Hm-TPA hemi-cryptophane bearing a tris(2-pyridylmethyl)amine (TPA) moiety was prepared (Scheme 1). The air-stable Cu(II)(Hm-TPA)(ClO₄)₂ complex was obtained by reacting Hm-TPA with 1 equiv of copper(II) perchlorate at room
temperature in acetone. The metalation occurred immediately, and the encaged complex was precipitated with diethyl ether, isolated by filtration, and characterized by ESI-HRMS (Figure S1), UV–vis (Figure S2), and EPR (Figure S3). In agreement with the simulated spectrum, the experimental EPR spectrum of CuII(Hm-TPA)(ClO4)2 in CH2Cl2 reveals the presence of two Cu(II)-based species in solution, caused by two different tetragonal distortions. The first one, accounting for 15% of the global signal, corresponds to an elongated distortion (d2−d3), which is axial (g = [2.270 2.090 2.090], and a = [150 0 0] × 10−4 cm−1). The second one, accounting for 85% of the global signal, corresponds to a compressed distortion (d13), which is orthorhombic (g = [2.244 2.120 1.987], and a = [0 57 167] × 10−4 cm−1).24

After replacement of perchlorate anion with triflate, the complex CuII(Hm-TPA)(SO3CF3)2 afforded single crystals suitable for X-ray diffraction analysis (Figure 1). The structure of the caged complex shows one copper center that adopts a trigonal bipyramidal geometry, wherein the trigonal plane comprises the three pyridine nitrogen atoms (N1–N3). The axial positions are occupied by the tertiary amine nitrogen (N4) and an acetonitrile molecule, which is pointing toward the inside of the Hm-TPA cavity. A well-defined cavity, encaging a second molecule of acetonitrile, is observed just above the copper center, attesting to an endohedral functionalization of the hemicycrophane, which simultaneously hosts the metal ion in its southern part (TPA unit) and one guest molecule (CH2CN) in its northern cavity (CTV unit).

The related iron complex FeII(Hm-TPA)(ClO4)2 was prepared by reacting Hm-TPA with 1 equiv of iron(II) perchlorate at room temperature in acetonitrile. The metalation occurred immediately, and the encaged complex was precipitated with diethyl ether, isolated by filtration, and characterized by ESI-HRMS (Figure S4) and UV–vis (Figure S5). The 1H NMR spectra of the FeII(Hm-TPA)(SO3CF3)2 complex recorded in CD3CN at 298, 270, 260, and 240 K exhibit downfield resonances when compared to those of the free ligand, attesting to a low-spin Fe(II) state in agreement with the reported 1H NMR characterization of the model complex FeII(TPA)(SO3CF3)2 (Figures S6 and S7).25

Compared to those of the C2 symmetrical Hm-TPA ligand (Figure S6, top), the signals of FeII(Hm-TPA)(SO3CF3)2 appeared to be broader and split, indicating a loss of cage symmetry due to a metal center in an octahedral geometry (Figure S6, bottom) [expected for low-spin (LS) Fe(II) complexes]. This behavior differs from that of the model complex FeII(TPA)(SO3CF3)2, which displays an effective 3-fold symmetry in solution due to the fast exchange process that averages the environment of the three pendant pyridines on the NMR time scale.25 Clearly, the more rigid supramolecular structure found in FeII(Hm-TPA)(SO3CF3)2 inhibits these fast exchange processes.

Encapsulation of Methane inside the Hemicycrophane Cavity. Cryptophanes are CTV-based homotopic capsules, which have been reported as efficient receptors for CH4.26 On the other hand, a C2 symmetrical covalent molecular cage based on the TPA ligand has very recently been used by Bajić and co-workers for the trapping of small hydrophobic molecules, including CH2Cl2 and methane.27 The hemicycrophane Hm-TPA is a heteroditopic derivative of cryptophane, built from a CTV unit (northern part) and a TPA ligand (southern part). We therefore investigated the ability of Hm-TPA to engage host–guest interaction with small hydrophobic substrates such as CH2Cl2 and CH4. Single crystals of Hm-TPA, suitable for X-ray diffraction, were obtained by slow diffusion of Et2O in a CH2Cl2 solution of the cage. Interestingly, the corresponding XRD structure reveals one encaged CH3Cl molecule, which appears to be wrapped by the C2 structure of Hm-TPA. This observation confirms the ability of the hydrophobic pocket of Hm-TPA to bind small hydrophobic guests in the solid state. We then investigated the interaction between Hm-TPA and CH4 by 1H NMR using C2D2Cl4 as the solvent.28 Upon methane bubbling, the signals of some aromatic protons of the CTV and TPA moieties of Hm-TPA display moderate high-field shifts (Figure 2a, signals a–c, g, and h), while aromatic protons corresponding to the phenyl spacers (Figure 2a, signals e and f) exhibit slightly more marked downfield shifts, attesting to the interaction of one (or more) molecule of CH4 with the host Hm-TPA (Table S1). Furthermore, the high-field shift (1.92 Hz) of the CH4 resonance observed in the presence of Hm-TPA (Figure 2d) is in good agreement with its encapsulation within the hemicycrophane cavity. It should be noted, however, that the observed shifts remain modest, indicating a weak interaction in C2D2Cl4 which might result from (i) a fast exchange process between bound and free CH4 molecules at 298 K or (and) (ii) the competitive encapsulation of this hydrophobic solvent.

Oxidation of Methane. We then investigated the reactivity of different catalytic sites in the oxidation of methane. The influence of the metal (Cu, V, or Fe), the first coordination sphere provided by the non-heme ligand, and the hemicycrophane structure was probed using the complexes shown in Scheme 1.

Methane, having very inert C–H bonds with a bond dissociation energy (BDE) of 104.9 kcal mol−1, can be oxidized only by strong oxidizing species. When organic solvents...
typically containing more active C–H bonds are used, e.g., CH₃CN and CH₂Cl₂, their oxidation and the formation of C₁ oxidation products cannot be excluded because the organic solvent is in a huge excess with respect to dissolved CH₄, typically in the millimolar concentration range. To avoid possible oxidation of organic solvents by the metal-based oxidizing species that would mask the target reaction, the oxidation of CH₄ was studied in water. To this end, the complexes were supported on silica and applied in heterogeneous oxidation of methane by H₂O₂, a clean and industrially relevant oxidant. It is noteworthy that this oxidant can also be used by monoxygenases for the generation of active high-valence metal–oxo species via shunted pathways. The reactions were performed in slightly acidic water (0.07 M H₂SO₄) for 20 h at 60 °C using an autoclave containing 50 mg of a SiO₂-supported catalyst (1 μmol of complex) and 0.33 M H₂O₂ oxidant, and the mixtures charged with methane (30 bar).²⁹ The catalytic performances of “encaged” and “naked” catalysts were evaluated by the direct comparison of (i) the selectivity for primary oxidation products (percentage of CH₃OH and CH₃OOH produced with respect to the total amount of oxidized products) and (ii) the turnover number (TON, micromoles of oxidation products per micromole of catalyst).

### RESULTS

#### Copper Complexes.

In the initial experiments, the tris(2-aminoethyl)amine (TREN) copper-based supramolecular complex Cu²⁺(Hm-TREN)(ClO₄⁻)₂ and its “naked” analogue Cu²⁺(TREN)(ClO₄⁻)₂ (Scheme 1) were compared in the heterogeneous oxidation of CH₄ by H₂O₂. The positioning of the hemicryptophane hydrophobic cavity above the Cu²⁺-based active site of Cu²⁺(Hm-TREN)(ClO₄⁻)₂ has recently been described as an efficient strategy for enhancing the activity and selectivity of cyclohexane oxidation. Higher product yields and an increase in the selectivity for cyclohexanol were observed.¹⁹ This improvement originates from the positive conjunction of two factors. (i) The supramolecular architecture better protects the catalyst from oxidative degradation because another catalyst molecule cannot fit inside the hemicryptophane cavity and access the active species, and (ii) the affinity of the hemicryptophane host for hydrophobic cyclohexane is higher than that of the more hydrophilic cyclohexanol. However, when applied to the oxidation of CH₄, caged Cu²⁺(Hm-TREN)(ClO₄⁻)₂ and “naked” Cu²⁺(TREN)-(ClO₄⁻)₂ display low TONs of 1.8 and 0.6, respectively,

![Figure 2. (a) Diagram of the X-ray crystal structure of CH₂Cl₂ ⊂ Hm-TPA with space-filling representation of CH₂Cl₂ (left) and HmTPA (right). (b) Partial ¹H NMR spectra (C₂D₂Cl₄, 300 MHz) of the cage Hm-TPA at 298 K before (top) and after (bottom) bubbling of methane (3 equiv). (c) Schematic representation of the cage Hm-TPA. (d) ¹H NMR resonance of CH₄ in C₂D₂Cl₄ in the absence (top) and presence (bottom) of Hm-TPA.](image)

![Table 1. Oxidation of CH₄ by H₂O₂ Catalyzed by Supported Copper(II) Complexes](table)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>HCOOH¹ TON</th>
<th>HCHO¹ TON</th>
<th>CH₃OH¹ TON</th>
<th>CH₃OOH⁴ TON</th>
<th>Total⁴ TON</th>
</tr>
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<tr>
<td>Cu⁰(TREN)</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
<td>0.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Cu⁰(Hm-TREN)</td>
<td>1.3</td>
<td>0.2</td>
<td>–</td>
<td>0.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Cu⁰(Hm-TPA)</td>
<td>1.4</td>
<td>0.1</td>
<td>–</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Cu⁰(Hm-TREN-COO⁻)</td>
<td>0.7</td>
<td>–</td>
<td>–</td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>

¹Reaction conditions: reaction time of 20 h, 60 °C, solvent of H₂O, 2 mL; 0.33 M H₂O₂, 0.07 M H₂SO₄, P(CH₄) = 30 bar, 50 mg of silica-supported catalyst containing 1.0 μmol of complex. ²TONs of CH₃OH, CH₃OOH, and HCOOH were determined by ¹H NMR and are the average of at least three experiments. ³The yield of HCHO was determined by the Nash colorimetric method. ⁴Moles of (CH₃OH + CH₃OOH + HCOOH + HCHO)/moles of catalyst. The estimated error for the TON was ±20%. ⁵Reaction time of 20 h, 60 °C, solvent of H₂O, 2 mL; 0.33 M H₂O₂, 0.07 M H₂SO₄, P(CH₄) = 30 bar, 50 mg of silica-supported catalyst containing 1.0 μmol of complex. ⁷TONs of CH₃OH, CH₃OOH, and HCOOH were determined by ¹H NMR and are the average of at least three experiments. ⁸The yield of HCHO was determined by the Nash colorimetric method. ⁹Moles of (CH₃OH + CH₃OOH + HCOOH + HCHO)/moles of catalyst. The estimated error for the TON was ±20%.

![Figure 2. (a) Diagram of the X-ray crystal structure of CH₂Cl₂ ⊂ Hm-TPA with space-filling representation of CH₂Cl₂ (left) and HmTPA (right). (b) Partial ¹H NMR spectra (C₂D₂Cl₄, 300 MHz) of the cage Hm-TPA at 298 K before (top) and after (bottom) bubbling of methane (3 equiv). (c) Schematic representation of the cage Hm-TPA. (d) ¹H NMR resonance of CH₄ in C₂D₂Cl₄ in the absence (top) and presence (bottom) of Hm-TPA.](image)
indicating the difficulty of reaching an efficient CH4 oxidation using the TREN-CuII active site in combination with H2O2 (Table 1). Nevertheless, the supramolecular complex CuIII(Hm-TREN)(ClO4)2 provided a TON 3-fold higher than that of “naked” CuII(TREN)(ClO4)2 (Table 1). This positive confinement effect is in line with the results obtained in the cyclohexane oxidation.15 Unfortunately, the low yields of oxidized products preclude the direct comparison of the selectivity of these complexes for CH3OH and CH3OOH. Similarly, the CuII(Hm-TKA)(ClO4)2 complex showed a low activity in methane oxidation (TON = 1.5).

Thus, no significant changes in reactivity were observed upon replacement of the three amine functions of the TREN ligand with the more withdrawing pyridine units. The related water-soluble cage complex CuIII(Hm-TREN-COO−), an analogue of CuIII(Hm-TREN) in which the methoxy groups of the CTV moiety are replaced by three carboxylate groups, was then studied as a homogeneous catalyst. When applied under identical catalytic conditions, but in a homogeneous fashion, CuIII(Hm-TREN-COO−) displays a catalytic efficiency that is lower than that of its silica supported counterpart, CuIII(Hm-TREN), with total TONS of 0.7 and 1.8, respectively (Table 1). These results confirm that the higher catalytic efficiency observed for the silica-supported catalyst cannot arise from a leaching of the catalyst from the silica. The sluggish oxidation of CH4 mediated by catalytic amounts of CuII(Hm-TREN)(ClO4)2, CuII(Hm-TREN-COO−), and CuII(Hm-TPA)(ClO4)2, might be explained by the nature of the active site. Although the involvement of the Cu(III) oxidation state in biological and biomimetic oxidation processes has been documented,30 the activation of H2O2 at Cu(II) centers can lead to the generation of HOO* and HO* radicals in a Fenton-like fashion.31 Therefore, in the presence of a recalcitrant methane molecule, the freely diffusing HOO* or/and HO* species might react preferentially with the weaker C−H bonds found in the hemicryptophane scaffold, resulting in the degradation of the complexes. This hypothesis was confirmed by ESI-MS analysis of the CuII(Hm-TPA) solution in CH3CN after addition of H2O2, where signals with m/z values corresponding to the oxidized complex were observed (Figure S8).

Vanadium Complexes. Oxido−vanadium(V) hemicryptophane complexes bearing a trialkanol amine coordination unit (TKA) have recently been described as efficient catalysts for sulfoxidation reactions.20,22 Indeed, supramolecular V(V)-based complexes V(Hm-TKA) and V(Hm-BINOL-TKA) have shown enhanced selectivity, reactivity, and turnover numbers compared to those of their related model complex V(TKA) that is devoid of the cavity. This strong confinement effect, derived from the hydrophobic cavity present in these flexible systems, allows for both hydrophobic substrate recognition and hydrophilic product release. On this basis, we have first focused on exploring the ability of oxido−vanadium supramolecular complexes to oxidize methane. The importance of having a second coordination sphere is well emphasized by comparing the supramolecular catalyst V(Hm-TKA) and its “naked” analogue V(TKA) (Figure 3 and Table S1). The introduction of a hydrophobic cavity above the metal site leads to an increase in the yield of CH3OH and CH3OOH (Table 2). Importantly, similar TONS of 6.6 and 7.4 were found using V(Hm-TKA) and V(TKA), respectively, indicating that the caged catalyst did not suffer from undesired product inhibition, which is commonly observed for supra-

Figure 3. Structures of oxido−vanadium complexes and comparison of their TONS and selectivities to those of the initial oxidation products of methane. Footnote a: moles of (CH3OH + CH3OOH + HCOOH + HCHO)/moles of catalyst. Footnote b: (CH3OH + CH3OOH)/(CH3OH + CH3OOH + HCOOH + HCHO) × 100. For reaction conditions, see Table 1.
That the efficiency of the supramolecular complex was also 2 times higher than that of the model complex $\text{Fe}^{II}(\text{TPA})-(\text{ClO}_4)_2$ that is devoid of a cavity ($\text{TON} = 4.7$ (Table 3)).

Although the absolute yields of the over-oxidized products formaldehyde and formic acid appear to be enhanced by a factor of 1.7 when the supramolecular catalyst was used [$\text{TON}_{\text{HCHO+HCOOH}} = 4$ and 6.7 for $\text{Fe}^{II}(\text{TPA})$ and $\text{Fe}^{II}(\text{HmTPA})$, respectively], these values are not indicative of the reaction selectivity. Indeed, the selectivity toward the primary product was determined by looking at the ratio of mono-oxidized ($\text{CH}_3\text{COOH}$ and $\text{CH}_3\text{OH}$) to over-oxidized ($\text{HCOOH}$ and $\text{HCHO}$) products (see Figure 4). The analysis of the oxidation products revealed a 2-fold enhanced selectivity toward $\text{CH}_3\text{OH}$ and $\text{CH}_3\text{OOH}$ for the caged catalyst

![Figure 4. Comparison of TON and selectivity toward primary products of methane oxidation for iron catalysts $\text{Fe}^{II}(\text{Hm-TPA})$-($\text{CO}_4)_2$ and $\text{Fe}^{II}(\text{TPA})$-($\text{CO}_4)_2$. Footnote a: moles of ($\text{CH}_3\text{OH} + \text{CH}_3\text{OOH} + \text{HCOOH} + \text{HCHO}$)/moles of catalyst. Footnote b: ($\text{CH}_3\text{OH} + \text{CH}_3\text{OOH}$)/($\text{CH}_3\text{OH} + \text{CH}_3\text{OOH} + \text{HCOOH} + \text{HCHO}$) $\times$ 100. For reaction conditions, see Table 1.](image-url)
Fe$^{II}$(Hm-TPA)(ClO$_4$)$_2$ (27% selectivity) compared to that of the “naked” complex Fe$^{II}$(TPA)(ClO$_4$)$_2$ (15% selectivity). This selectivity in primary oxidation products was the highest observed among all bioinspired complexes screened during this study. Thus, the oxidation of CH$_4$ mediated by Fe$^{II}$(Hm-TPA)(ClO$_4$)$_2$ was reinforced by a strong confinement effect. The incorporation of the hydrophobic cavity above the TPA–iron(II) active center enhances the yield of mono-oxidized products by a factor of 3.6 with TON$_{CH_3OH}$ and TON$_{CH_3OOH}$ values of 2.5 and 0.7 for Fe$^{II}$(Hm-TPA)(ClO$_4$)$_2$ and Fe$^{II}$(TPA)(ClO$_4$)$_2$, respectively (Figure 4 and Table 3). Such a confinement effect can be explained by the existence of host–guest interaction between CH$_4$ and the hemicryptophane hydrophobic cavity, leading to (i) proximity between the substrate and active site and (ii) release of the hydrophilic oxidized products (CH$_3$OH and CH$_3$OOH) from the hemicryptophane hydrophobic cage. Importantly, similar behaviors are reported for the oxidation of cyclohexane, and thiaanisol, inside the hydrophobic cavity of hemicryptophane-based catalysts.

**DISCUSSION**

In this study, a novel strategy for the development of bioinspired catalysts for the oxidation of methane to methanol was proposed and evaluated. To combine a reactive metal catalytic site with an adjacent hydrophobic pocket for methane binding, a series of iron, vanadium, and copper complexes supported by trialkanolamine, tren, and tris(2-pyridylmethyl)amine ligands bearing hemicryptophane moieties was prepared. The interaction of methane with hydrophobic cages of Hm-TPA was observed by the $^1$H NMR method. We have shown that the positioning of a hemicryptophane hydrophobic cavity above a metal-based oxidizing center positively influences the way that methane C–H bonds are catalytically oxidized by H$_2$O$_2$. Indeed, the functional duality of the hemicryptophane structure allows for host–guest interactions with hydrophobic substrates inside its well-defined cavity (northern part), along with the simultaneous coordination of biologically relevant V$^{V}$, Cu$^{II}$, and Fe$^{III}$ metal ions (southern part). The heterogeneous catalytic oxidation of methane in water has been studied through the screening of six vanadium-, copper-, and iron-based silica-supported complexes bearing a supramolecular second coordination sphere. Although the cage compounds could not be recycled because of progressive decomposition during the reaction [as observed for the Cu$^{II}$(Hm-TPA) complex (Figure S8)], the effect of confinement on CH$_4$ oxidation has been unambiguously shown through the direct comparison between “encaged” and “naked” complexes. Such catalyst breakdown accompanied by the known decomposition of H$_2$O$_2$ into H$_2$O and O$_2$ leads to undesired H$_2$O$_2$ consumption that justifies the elevated amounts of H$_2$O$_2$ required to convert methane in our catalytic systems. Although copper-based complexes were found to be rather sluggish catalysts, their iron(II) and vanadium(V) analogues display promising catalytic efficiencies with total TONs ranging from 4.7 to 18.3. It was found that the supramolecular complexes simultaneously holding an oxido–vanadium active center, binaphthyl spacers, and either CTV (hydrophobic cavity, Hm-BINOL-TKA) or a benzene unit (open hydrophobic pocket, Bz-BINOL-TKA) were the most efficient catalysts with total TONs of 13.2 and 18.3, respectively. However, these improved catalytic efficiencies were associated with an undesired decrease in selectivity toward initial oxidation products. Thus, it appears that in these cases the molecular cage catalysts show a higher efficiency also favoring the over-oxidation of methane, as supported by the TON in over-oxidation products. This highlights how challenging it is to develop catalytic systems featuring both high activity and selectivity in methane oxidation. On the other hand, the confinement effect observed for hemicryptophane complex V(Hm-TKA) (where binaphthyl spacers are replaced by phenyl moieties) results in improved selectivity, while its catalytic efficiency remains similar to that of its parent model complex. Remarkably, controlling the microenvironment above a non-heme iron(II)(TPA) active site clearly improves both the efficiency and the selectivity of the catalytic oxidation of CH$_4$. The intrinsic inertness of methane compared to its mono-oxidized analogues (such as methanol) makes the single oxidation of CH$_4$, a particularly challenging task. Although formic acid is the major product with all of the cage complexes tested, a strong improvement in selectivity is observed using the new supramolecular catalyst Fe$^{II}$(Hm-TPA). Indeed, the yield in target mono-oxidized products (CH$_3$OH and CH$_3$OOH) was successfully increased (by 3.6-fold) compared to that of its “naked” model. We propose that such a confinement effect arises from the encapsulation of CH$_4$ within the organic hydrophobic cavity located above the iron(II) catalytic center, along with the release of the more hydrophilic mono-oxidized products to the bulk solution. To the best of our knowledge, this represents the first example of methane oxidation catalyzed by well-defined bioinspired catalysts inside the cavity of a molecular receptor.

**CONCLUSION**

The results obtained in this study highlight the relevance of the hemicryptophane nanoreactors, which can be used as homogeneous or heterogeneous supported catalysts. These functional models combine the efficiency of heterogeneous catalysis (in pure water) with the convenient character of homogeneous systems (host–guest studies). Therefore, the confinement of well-defined metal-based active centers that can activate the green and cheap H$_2$O$_2$ oxidant should be considered as a promising strategy for the further development of highly active catalysts for the selective oxidation of methane to methanol. Finally, in contrast to sluggish copper(II) complexes, the encouraging results obtained with the iron(II)-based catalysts might account for the involvement of a high-valence metal-based oxidant in a manner similar to that involved for enzymatic systems (MMO). Future work will be focused on the preparation of a catalyst with improved oxidizing activity and stability.


(28) This solvent (108 Å³) is much larger than CH₄ (33 Å³), weakening the competitive interaction between the solvent and the cavity of Hm-TPA.

(29) Control experiments were performed in the absence of CH₄, which produced a small quantity of oxidized products due to degradation of the organic ligand. Tables 1−3 give the corrected values of TON in oxidized products due to methane oxidation, i.e., after subtraction of the amounts of products obtained during the control experiments (without CH₄). We could not detect CO₂ by our analytical tools, although the formation of small amounts of CO₂ cannot be excluded.


