# Catalysis Science & Technology

## Accepted Manuscript

This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

*Accepted Manuscripts* are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard **Terms & Conditions** and the **ethical guidelines** that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.

RSC Publishing

www.rsc.org/catalysis
Registered Charity Number 207890

Catalysis Science & Technology RSCPublishing

Full Paper

Cite this: DOI: 10.1039/x0xx00000x

DOI: 10.1039/x0xx00000x

www.rsc.org/

# Developing an efficient catalyst for controlled oxidation of small alkanes under ambient conditions

Penumaka Nagababu, Steve S.-F. Yu, Suman Maji, Ravirala Ramu and Sunney I. Chan*

The tricopper complex [$Cu^ICu^ICu^I$(**7-N-Etppz**)]$^{1+}$, where **7-N-Etppz** denotes the ligand 3,3´-(1,4-diazepane-1,4-diyl)bis[1-(4-ethyl piperazine-1-yl)propan-2-ol], is capable of mediating facile conversion of methane into methanol upon activation of the tricopper cluster by dioxygen and/or $H_2O_2$ at room temperature. This is the first molecular catalyst that can catalyze selective oxidation of methane to methanol without over-oxidation under ambient conditions. When this $Cu^ICu^ICu^I$ tricopper complex is activated by dioxygen or $H_2O_2$, the tricopper cluster harnesses a “singlet oxene”, the strongest oxidant that could be used to accomplish facile O-atom insertion across a C−H bond. To elucidate the properties of this novel catalytic system, we examine here the methane oxidation over a wider range of conditions and extend the study to other small alkanes including components of natural gas. We illustrate how substrate solubility, substrate recognition and the amount of $H_2O_2$ used to drive the catalytic oxidation can affect the outcome of the turnover, including regio-specificity, product distributions and yields of substrate oxidation. These results will help to design another generation of the catalyst to alleviate the limitations of the present system.

## Introduction

Planet earth has enormous reserves of methane ($CH_4$), which can be harnessed by transformation into methanol ($CH_3OH$).[1] $CH_3OH$ is well established as a valuable commodity, both itself as a transportable fuel and as a source for derived chemicals, including $H_2$.[2] However, the controlled oxidation of $CH_4$ to $CH_3OH$ is challenging.[3] To begin with, the C−H bond in $CH_4$ is extremely inert due to its high bond-dissociation energy (105 kcal/mole).[3,4] In addition, the product $CH_3OH$ is prone to further oxidation to form other products.[5] Nevertheless, effective utilization of this valuable resource is not only economically advantageous, but also environmentally beneficial, as $CH_4$ is also a major contributor to global warming.[6]

Methane monooxygenases (MMO) are known to mediate efficient oxidation of $CH_4$ to $CH_3OH$ in methanotrophic bacteria under ambient conditions of temperature and pressure.[7] The membrane-bound particulate methane monooxygenase (pMMO) is multicopper protein.[8,9] The soluble methane monooxygenase (sMMO) is a non-heme iron protein.[10,11] Both systems exploit metal clusters to catalyze this difficult chemistry. Although there have been a number of x-ray crystal structures on these proteins,[12,13,14] progress toward understanding how the metal clusters in these enzymes mediate this process has been slow, and attempts to develop functional mimics of these catalytic centers have met with only limited success.[15]

Recently, we have reported that the tricopper complex with the peptide HIHAMLTMGDWD derived from the PmoA subunit of pMMO from *Methylococcus capsulatus* (Bath)[14] is capable of mediating efficient epoxidation of propene to propene oxide and hydroxylation of $CH_4$ to $CH_3OH$ when the $Cu^ICu^ICu^I$-peptide complex is activated by $O_2$. Inspired by these results, we have developed biomimetic models of the tricopper cluster for alkane oxidation. Various trinucleating ligands have been designed and prepared to support a triad of $Cu^I$ ions and these tricopper complexes have been shown to be capable of mediating efficient oxidation of small organic substrates when the fully reduced tricopper cluster is activated by dioxygen and/or hydrogen peroxide.[16-19] In particular, the tricopper complex [$Cu^ICu^ICu^I$(**7-N-Etppz**)]$^{1+}$, where **7-N-Etppz** stands for the organic ligand 3,3´-(1,4-diazepane-1,4-diyl)bis[1-(4-ethylpiperazine-1-yl)propan-2-ol] (**Scheme 1**), mediates the facile conversion of $CH_4$ to $CH_3OH$ in acetonitrile (MeCN) at room temperature when the tricopper cluster is activated by dioxygen ($O_2$).[16] Moreover, the oxidation can be rendered catalytic when the fully reduced tricopper complex is regenerated by two-electron reduction of the partially oxidized tricopper complex by a molecule of $H_2O_2$. This is the first molecular catalyst that can catalyze the selective oxidation of $CH_4$ to $CH_3OH$ at ambient conditions.

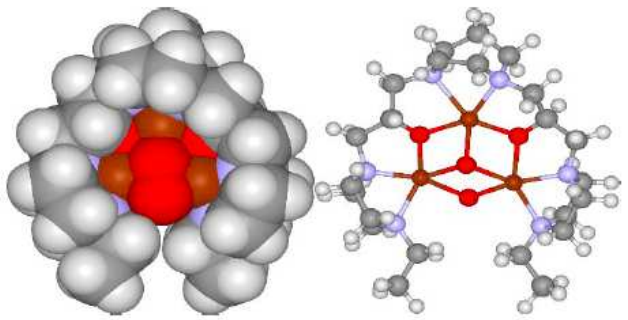
Following up on our earlier communication, we now examine the methane oxidation over a wider range of conditions than heretofore been carried out in order to delineate the factors influencing the turnover frequency (TOF) of the catalyst and the turnover number (TON). We also extend the study to other small alkanes including

---

*Academia Sinica, Institute of Chemistry, 128 Sec. 2, Academia Road, Nankang, Taipei 11529, Taiwan. Email: sunneychan@yahoo.com; Fax: +886-2-2783-1237; Tel: +886-2-2789-8654*

Electronic Supplementary Information (ESI) available: preparation of catalyst, GC analysis of oxidation products and control experiments. See DOI: 10.1039/b000000x/

components of natural gas including ethane, propane and butane. We study the effects of substrate recognition, substrate concentration, the effects of futile cycles on the outcome of the substrate oxidation, including regio-specificity, product yields and distribution, as well as the overall turnover frequency of the substrate oxidation.



**Scheme 1** The tricopper complex [$Cu^ICu^ICu^I$(**7-N-Etppz**)]$^{1+}$, where **7-N-Etppz** stands for the organic ligand 3,3´-(1,4-diazepane-1,4-diyl)bis[1-(4-ethylpiperazine-1-yl)propan-2-ol]. Color code- white: hydrogen; grey: carbon; blue: nitrogen; red: oxygen; brown: copper.

## Experimental methods

### Materials

The synthesis and spectroscopic characterization of the **7-N-Etppz** ligand as well as the preparation of the [$Cu^ICu^ICu^I$(**7-N-Etppz**)]($ClO_4$) complex have been described earlier.[16] When the $Cu^ICu^ICu^I$ complex is treated with $O_2$ in the absence of substrate, it forms the [$Cu^{II}Cu^{II}$(μ-O)$Cu^{II}$(**7-N-Etppz**)]($ClO_4$)$_2$ species, the same fully oxidized "dead-end" species previously reported for all tricopper complexes of this series.[17-19]

### Oxidation of alkanes under ambient conditions

22.7 μmoles (1 equiv.) of [$Cu^ICu^ICu^I$(**7-N-Etppz**)]$^{1+}$ are used to catalyze the oxidation of various hydrocarbons by $H_2O_2$ in 3 ml of MeCN (or EtCN) in a 60 ml glass sample bottle at room temperature. As the reduced tricopper complex is extremely air sensitive, it is necessary to perform the substrate oxidation experiments under a purified nitrogen atmosphere inside the glove box. The reaction mixture is vigorously stirred with a magnetic stirring bar for various times up to 1 h using different sample bottles. At designated intervals, a sample bottle is removed from the glove box to identify the products and determine the product yields by GC (see Supporting Information for details). 3 μl of nitrobenzene is added to the solution to provide an internal standard (IS) for quantitation of the products (Fig. S2). Control experiments are described in the Supporting Information (Fig. S3 and Table S1).

Of the various hydrocarbons studied, *n*-pentane, *n*-hexane, cyclohexane, and cyclohexene are liquids. Although each of these liquid substrates is not miscible with MeCN in all proportions, it has sufficient solubility and the substrate oxidation could be initiated by adding appropriate amounts of the hydrocarbon to the solvent containing the tricopper catalyst followed by adding the desired amounts of $H_2O_2$, and the solution is mixed vigorously. The data for these hydrocarbons are obtained with 11.3 mmoles (500 equiv.) of the hydrocarbon in each case and the turnover is driven by 200 equiv. of $H_2O_2$ from a 33% aqueous solution in the experiment.

In the case of $CH_4$, ethane, propane and *n*-butane, the glass sample bottle is first sealed tightly with a rubber cap and evacuated before one of these gas substrates (100 ml NTP or 4.17 × $10^{-3}$ mole, ~200 equiv,) is injected into the solvent containing the tricopper catalyst using a gas syringe. 2.27 mmoles of $H_2O_2$ (100 equiv.) from a 33% aqueous solution is then injected using a separate syringe to initiate the oxidation of ethane, propane or *n*-butane. Again, the reactions are carried out with vigorous agitation of the solution. In the case of $CH_4$, 0.39 mmoles (20 equiv.) of $H_2O_2$ are used and the $H_2O_2$ solution is added dropwise over 2-3 min. Given the limited solubility of these hydrocarbon gases in MeCN, the extent of hydrocarbon oxidation depends on the gas pressure in the overhead space (starting pressure 1.67 atm), as well as the amount of the gas dissolved in the solution. With the low solubility of $CH_4$ in MeCN, we use only 20 equiv. of $H_2O_2$ in the initial experiments to mitigate abortive cycling of the catalyst. The amounts of $H_2O_2$ added have a dramatic effect on the turnover, as demonstrated by performing the $CH_4$ oxidation using 20, 40, 60 and 80 equiv. of $H_2O_2$, as well as incremental additions of $H_2O_2$ over the time course of the experiment initiated with 20 equiv. of $H_2O_2$.

### Oxidation of other substrates

The [$Cu^ICu^ICu^I$(**7-N-Etppz**)]$^{1+}$ complex is also used to mediate the oxidation of $CH_3OH$, ethanol, isopropanol, and 2-butanol by $H_2O_2$. These experiments are performed with 200 equiv. of $H_2O_2$ from 35 % aqueous solution, 500 equiv. of substrate, and one equiv. (22.7 μmoles) of the tricopper complex in MeCN (total volume 3 ml) at room temperature for 1 h.

## Results and discussion

We summarize in **Fig. 1** and **Table 1** the findings obtained when 1 equiv. (22.7 μmoles) of [$Cu^ICu^ICu^I$(**7-N-Etppz**)]$^{1+}$ is used to catalyze the oxidation of various hydrocarbons by $H_2O_2$ at room temperature under the conditions described in **Experimental methods**.

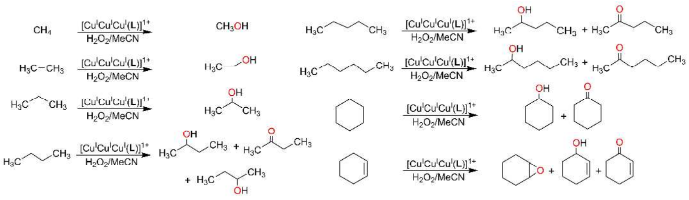


**Fig. 1** Oxidation of *n*-alkanes, cycloalkanes and cycloalkenes by $H_2O_2$ catalyzed by the tricopper complex [$Cu^ICu^ICu^I$(**7-N-Etppz)**]$^{1+}$at room temperature.

Only $CH_3OH$, ethanol, and 2-propanol are produced in the catalytic oxidation of $CH_4$, ethane, and propane mediated by the tricopper cluster, respectively. There is no evidence for over-oxidation of these hydrocarbons to form their corresponding aldehydes or ketones. In the case of *n*-butane, however, we observe the formation of 2-butanol, 2-butanone, and 2,3-butanediol. For *n*-pentane, the products are 2-pentanol and 2-pentanone, and for *n*-hexane, 2-hexanol and 2-hexanone, with preference for the ketone in both cases. With cyclohexane, cyclohexanol and cyclohexanone are formed in roughly equal proportions. For cyclohexene, the oxidation yields the epoxide, cyclohexanol and cyclohexanone, in favor of the epoxide and cyclohexanone.

The time courses of the oxidation of the various hydrocarbons are shown in **Fig. 2**, where we have plotted the equivalents of the oxo-products produced at various times up to one hour, weighted according to the number of oxidizing equivalents transferred (TON). These data reveal that the oxidation is indeed very rapid for all the hydrocarbons studied. In every case, the $H_2O_2$ used to drive the turnover is almost exhausted in less than 20 min, well before the completion of the one-hour study. This is true even in the case of $CH_4$.

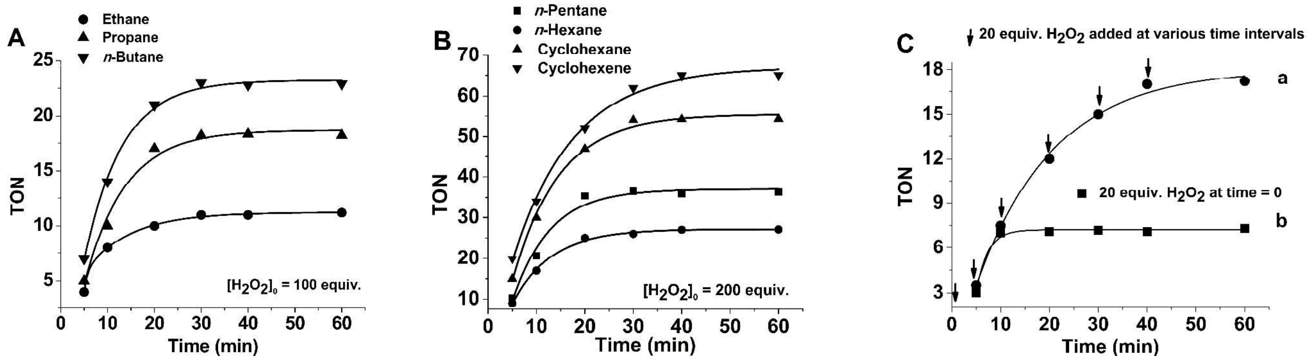


**Fig. 2** Time courses of the oxidation of various hydrocarbon substrates by $H_2O_2$ mediated by the $[Cu^ICu^ICu^I(\textbf{7-N-Etppz})]^{1+}$ complex. Shown in *panel* **A** are the results for ethane, propane, and *n*-butane; *panel* **B** summarizes the results for *n*-pentane, *n*-hexane, cyclohexane, and cyclohexene; and *panel* **C** depicts the results observed for methane under two different sets of conditions. See text for the experimental details.

## The catalytic cycle

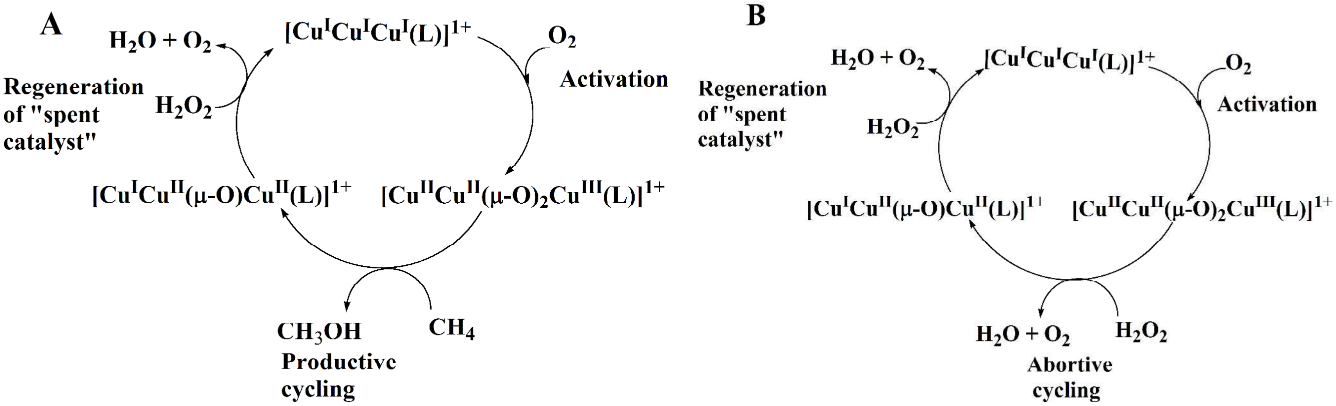
We depict in **Scheme 2** *panel* **A** the turnover cycle that we have previously proposed for the catalytic oxidation of $CH_4$ mediated by $[Cu^ICu^ICu^I(\textbf{7-N-Etppz})]^{1+}$ in the presence of $O_2$ and $H_2O_2$. Although we show here that the tricopper complex is activated by $O_2$, the activation could also be accomplished with two molecules of $H_2O_2$. Thus, the catalytic cycle can be carried out in the presence of $H_2O_2$ alone, as we have described earlier[18,19] and will demonstrate again here with the oxidation of alkane substrates. In either scenario, one additional molecule of $H_2O_2$ is required to serve as the "sacrificial" reductant to re-reduce the "spent" catalyst in order to regenerate the catalyst for another catalytic turnover. There is, however, more than a subtle difference between the two scenarios. In sufficiently high concentrations of $O_2$, $H_2O_2$ is no longer a good reductant and typically only a single turnover of the catalyst is observed with $O_2$ as the oxidant under these conditions. A different "sacrificial" reductant could, of course, be used to regenerate the catalyst.

**Scheme 2** *panel* **B** depicts abortive cycling of the catalytic system, a competing process that aborts the activated tricopper cluster by direct reduction with $H_2O_2$, the "sacrificial reductant" in this case. The activated tricopper cluster harnessing the "oxene" has a high redox potential so it can be aborted if the transfer of the harnessed O-atom to the substrate molecule is not sufficiently rapid. This process, which decreases the catalytic efficiency of the catalytic system, becomes operative when $k_{\text{abortive}}\,[H_2O_2] > k_{\text{OT}}\,[\text{substrate}]$, where $k_{\text{OT}}$ and $k_{\text{abortive}}$ denote the bimolecular rate constants for the "O-atom" transfer reaction from the activated tricopper cluster to the organic substrate and the abortive reduction, respectively, a scenario that obtains at high $H_2O_2$ or low substrate concentrations.

A measure of the effectiveness of the catalytic system for the oxidation of the various hydrocarbons examined in this study is given by the percentage of the $H_2O_2$ consumed by productive cycling for the amount of $H_2O_2$ used to drive the turnover. We define the catalytic efficiency by the ratio of the productive turnovers of the catalyst to the total number of turnovers of the catalyst including both productive and futile cycles during the course of the experiment. When the catalytic turnover is driven by $H_2O_2$ alone, 3 molecules of $H_2O_2$ are consumed for a productive cycle that leads to product formation and 4 molecules of $H_2O_2$ for an abortive turnover. These catalytic efficiencies are listed in the last column of **Table 1** for the various hydrocarbon substrates examined in this study under the conditions highlighted in columns 2 and 3. In this analysis, we have assumed that the total amount of $H_2O_2$ introduced into the medium to drive the substrate oxidation has been exhausted during the 1 h experiment, a good approximation when 200 equiv. of $H_2O_2$ are used. In any case, according to this indicator, the tricopper complex $[Cu^ICu^ICu^I(\textbf{7-N-Etppz})]^{1+}$ is indeed an efficient catalyst for the oxidation of hydrocarbons at room temperature.

## Catalytic efficiencies

Cyclohexane is the benchmark substrate for the type of catalytic reactions under discussion here.[18] The bond energy associated with the C-H bond is 99.5 kcal/mole, which is 5 kcal/mole lower than for $CH_4$. Under the conditions of our experiments, there is essentially no abortive cycling noted for this substrate. Time-course study indicates that practically all the $H_2O_2$ used to turn over the catalyst for substrate oxidation is consumed within 30 min (**Fig. 2**). Thus, the oxidation of cyclohexane to cyclohexanol and cyclohexanone mediated by the $[Cu^ICu^ICu^I($**7-N-Etppz**$)]^{1+}$ complex with $H_2O_2$ as the O-atom source is extremely efficient. Similar results have been obtained for this substrate with tricopper complexes supported by other trinucleating ligands.[18] No abortive cycling is observed with cyclohexene as well. This substrate is oxidized to cyclohexanol, cyclohexanone and the epoxide. Evidently, electrophilic *syn* addition of the O-atom across the C=C bond is more facile than direct C−H insertion. In any case, both cyclohexane and cyclohexene are sufficiently soluble in MeCN that $k_{OT}$ [substrate] > $k_{abortive}$ $[H_2O_2]$ under the conditions of the experiments.



**Scheme 2** Shown in *panel* **A** is the turnover cycle driven by $H_2O_2$ in the catalytic oxidation of $CH_4$ mediated by $[Cu^ICu^ICu^I($**7-N-Etppz**$)]^{1+}$ by $O_2$ and; *panel* **B** depicts abortive cycling of the catalytic system, a competing process that aborts the activated tricopper cluster by direct reduction with $H_2O_2$.

We have also observed a very high catalytic efficiency (98%) in our experiment on methane oxidation. However, here we have used only 20 equiv. of $H_2O_2$ to drive the turnover. With the lower amount of $H_2O_2$ employed to drive the oxidation, the TON is low. It also slows down the turnover of the tricopper catalyst. More importantly, however, the lower $H_2O_2$ concentration mitigates abortion of the activated catalyst, keeping more of the $H_2O_2$ for productive oxidative turnover, as evidenced by the high fraction of the $H_2O_2$ that is consumed by productive cycling of the catalyst. As expected, when greater amounts of $H_2O_2$ are used to oxidize the methane, the TON diminishes abruptly. With 40 equiv. of $H_2O_2$, the catalytic efficiency is only 30%, and with 80 equiv., only a meager 6% of the turnover of the catalyst results in the formation of methanol.

For methane, the factor limiting the turnover is the low solubility of the gas in MeCN. Higher amounts of $H_2O_2$ can be used if the concentration of $CH_4$ in the solution is higher to speed up the second-order O-atom transfer reaction mediated by the catalyst. Although there is an excess of $CH_4$ in the system, the methane concentration is limited by the solubility of the gas in the solvent under the headspace gas pressure. We have repeated the oxidation experiment with the volume of the solvent increased from 3 ml to 6 ml to ensure that the process is not limited by the availability of the hydrocarbon. The same amount of the tricopper catalyst is used and the same amount of $H_2O_2$ is used to drive the turnover. Thus, the concentration of the tricopper catalyst and the starting concentration of the $H_2O_2$ are now a factor of 2 lower, but the $CH_4$ concentration remains the same. Accordingly, the turnover should be slower, although the catalytic efficiency might be slightly improved. Essentially the same TON (~7) is obtained at the end of the 1 h experiment (**Fig. 2b** *panel* **C**). Thus, it is not the availability of $CH_4$ that is limiting the TON, rather the amount of $H_2O_2$ used to drive the process. To corroborate this conclusion, we add an additional 20 equiv. of $H_2O_2$ after 8-10 min when it is apparent that the initial amount has already been consumed. As expected, the turnover of the catalyst quickly proceeds to yield additional product, the TON rapidly doubling to ~12 within another 15 min (data not shown). In a separate experiment with same conditions, the methane oxidation is initiated with 20 equiv. of $H_2O_2$ (at 3 min), followed by incremental dropwise additions of 20 equiv. at 10 min, 20 min, 30 min, and 40 min, and a TON ~18 is eventually reached (**Fig. 2a** *panel* **C**). These observations clearly underscore the interplay between productive cycling and abortive cycling in the catalytic methane oxidation driven by $H_2O_2$. The catalytic efficiencies observed for the other substrates (ethane, propane, *n*-butane, *n*-pentane and *n*-hexane) reinforce this picture.

### The issue of over-oxidation

As noted earlier, $CH_4$, ethane and propane are oxidized only to $CH_3OH$, ethanol and 2-propanol, respectively. There is no evidence for any over-oxidation of these alkanes during the catalytic turnover. Consistent with this finding, $CH_3OH$, ethanol and 2-propanol are not found to be substrates of the catalytic system. When the $[Cu^ICu^ICu^I($**7-N-Etppz**$)]^{1+}$ complex is used to mediate the oxidation of these substrates with $H_2O_2$, there is no aldehyde or ketone detected by GC. The propensity to over-oxidation is one of the greatest challenges in the design of a catalyst for the conversion of $CH_4$ into $CH_3OH$. Thus, with the $[Cu^ICu^ICu^I($**7-N-Etppz**$)]^{1+}$ complex, we have achieved one of the main objectives in our development of a catalytic system for $CH_4$ hydroxylation.

In our design of the tricopper complex for $CH_4$ oxidation, we have built in a small molecular surface near the basal coppers of the triad for the recognition of the hydrophobic $CH_4$ molecule. This weak interaction facilitates the formation of a transient complex so that it can reach the transition state for the obligatory oxene transfer to oxidize the substrate when the tricopper cluster is activated. On the other hand, the binding surface is sufficiently small and hydrophobic that it is unable to accommodate the product $CH_3OH$ once the latter is formed. Evidently, this is true for ethane and propane as well. For these smaller alkanes, the product alcohols do not have sufficient binding affinity for the "active-site" pocket and are released as soon as the product is formed.

| **Substrate (C–H bond energy, kcal/mol)** | **Substrate (moles)** | **$H_2O_2$ (equiv.)**[a] | **Products (equiv.)** | | | **Catalytic turnovers (A+2B+2C)** | **Abortive cycles** | **Catalytic Efficiency**[b] **(%)** |
|---|---|---|---|---|---|---|---|---|
| | | | alkanol (**A**) | alkanone (**B**) | alkane diol (**C**) | | | |
| Methane (104.5) | $4.17\times10^{-3}$ | 20 | 6.5 | ---- | ---- | 6.5 | 0.125 | 98 |
| Ethane (101.1) | $4.17\times10^{-3}$ | 100 | 11 | ---- | ---- | 11 | 16.75 | 40 |
| Propane (100.4) | $4.17\times10^{-3}$ | 100 | 18.2 | ---- | ---- | 18.2 | 11.35 | 62 |
| *n*-Butane (98.2) | $4.17\times10^{-3}$ | 100 | 6 | 4 | 4.4 | 22.8 | 7.9 | 74 |
| *n*-Pentane (98) | $1.13\times10^{-2}$ | 200 | 1.2 | 13.8 | ---- | 28.8 | 28.4 | 50 |
| *n*-Hexane (98) | $1.13\times10^{-2}$ | 200 | 5.2 | 18 | ---- | 41.2 | 19.1 | 68 |
| Cyclohexane (99.3) | $1.13\times10^{-2}$ | 200 | 26 | 17 | ---- | 60 | 5 | 92 |
| **Substrate (C–H bond energy, kcal/mol)** | | | alkanol (**A**) | alkanone (**B**) | epoxide (**D**) | Catalytic turnovers (**A+2B+D**) | | |
| Cyclohexene **(83.9)** | $1.13\times10^{-2}$ | 200 | 4.2 | 21 | 18 | 64.2 | 1.85 | 97 |

[a] 1 equiv. of catalyst corresponds to 22.7 µmoles.

[b] Catalytic efficiency denotes the effectiveness of the $[Cu^ICu^ICu^I($**7-N-Etppz**$)]^{1+}$ complex as a catalyst for hydrocarbon oxidation based on the amount of $H_2O_2$ used to drive the turnover. It is given by the ratio of the productive turnovers of the catalyst to the total number of turnovers of the catalyst including both productive and futile cycles during the course of the 1-hour experiment.

This is apparently not the case with the alcohols formed with the higher alkanes. For example, in the case of *n*-butane, the 2-butanol evidently resides in the active site long enough for another round of oxidation to produce 2-butanone and the 2,3-butanediol. Since 2-butanol by itself is not a good substrate of the tricopper cluster for conversion to 2-butanone or 2,3-butanediol, the over-oxidation is evidently kinetically controlled. When 2-butanol is employed as the substrate in our catalytic system over the 1 h incubation experiment, only a very small amount of 2-butanone is formed (TON ~1). Surprisingly, with *n*-pentane, *n*-hexane, and cyclohexane, the alcohol is only further oxidized to give the ketone but the diol is not formed. This result suggests that the details of the interaction between the molecular binding surfaces of the tricopper complex and the substrate are important for the regio-specificity of the oxidation. For the longer alkanes, cyclohexane, and cyclohexene, van der Waals interactions between the aliphatic parts of the substrate and the binding surface of the activating tricopper cluster must dictate the positioning and orientation of these hydrocarbon substrates in the binding pocket. From examination of a CPK model of the activated tricopper complex together with models of various hydrocarbon substrates and their oxidized products, we surmise that the molecular surfaces on both the tricopper complex and the substrate/products dictate the specific van der Waals interactions and binding modes that lead to the regio-specificity observed in the oxidation.

### Turnover numbers (TON) and turnover frequencies (TOF)

With the catalytic system described here, the TON, or the amount of products formed during the time course of the experiment, is largely determined by the amounts of $H_2O_2$ used to drive the turnover of the tricopper catalyst after allowance is made for the catalytic efficiency. In principle, it is possible to increase the TON by using larger amounts of $H_2O_2$ or adding incremental amounts of $H_2O_2$ to the system at various times as we have demonstrated here. For example, when the $[Cu^ICu^ICu^I($**7-N-Etppz**$)]^{1+}$ complex is used to mediate the oxidation of cyclohexane, a TON of ~120 can be reached in this manner. However, as a batch process, water accumulates in the solution with increasing amounts of $H_2O_2$ solution added so that eventually the tricopper complex trashes out of solution. The catalyst is robust in MeCN containing small amounts of $H_2O$ otherwise.

We have estimated the turnover frequency (TOF) of the catalyst at early times when the $H_2O_2$ concentration $\approx [H_2O_2]_0$. The rate of turnover of the catalyst is limited by the regeneration of the "spent" catalytst after either a productive or abortive event, and it is directly proportional to the [$H_2O_2$] available at a particular instance. The TOF can be estimated from the rate of product formation at early times under conditions in which there is no abortive cycling. In the cases of cyclohexane and cyclohexene, for which the catalytic efficiencies approach unity, TOF ~ $10^{-1}$ $s^{-1}$. A TOF of ~5 ×$10^{-3}$ $s^{-1}$ is obtained when $CH_4$ is converted into $CH_3OH$ using 20 equivalents of $H_2O_2$. Were it possible to drive the oxidation of methane using 200 equiv. of $H_2O_2$ without significant abortive cycling, the TOF could be 10 times higher (~5 ×$10^{-2}$ $s^{-1}$). This analysis underscores the interplay between turnover rate and catalytic efficiency in the performance of the present catalytic system for the conversion of $CH_4$ to $CH_3OH$.

## Summary and outlook

In summary**,** the [$Cu^ICu^ICu^I$(**7-N-Etppz**)]$^{1+}$ catalyst promotes efficient oxidation of $CH_4$ as well as other small alkanes with $H_2O_2$ as the oxidant in MeCN at room temperature. The oxidation is regio-specific, and the turnover number is only limited by the amount of $H_2O_2$ used to drive the process under controlled conditions.

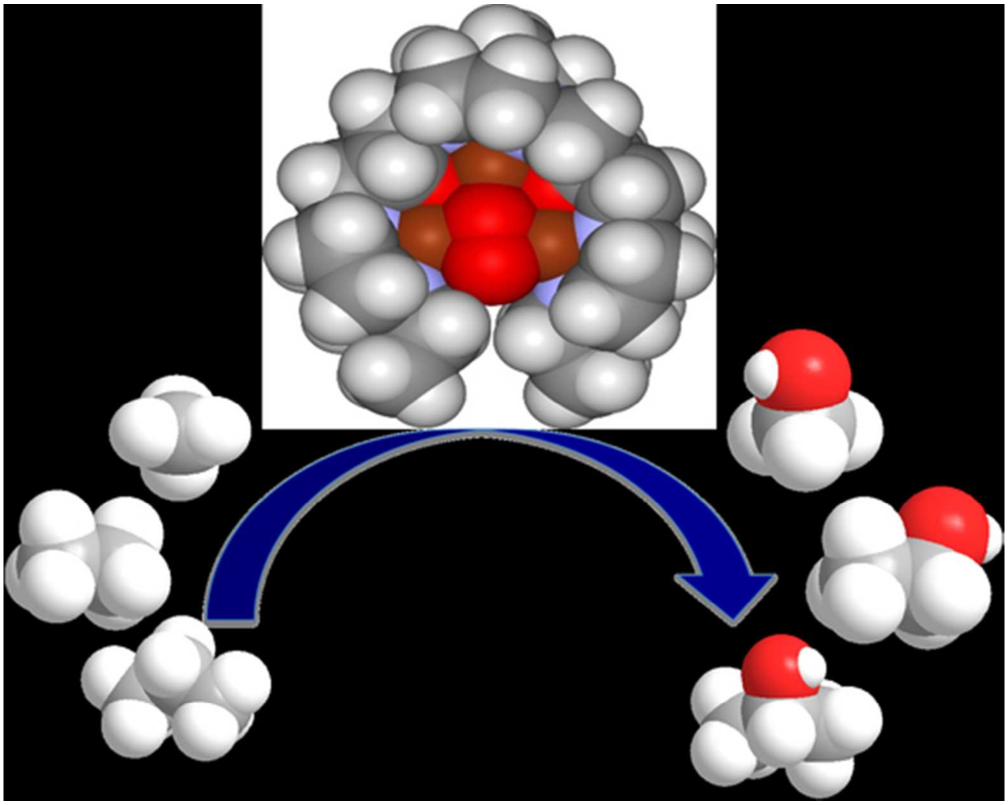
We have developed here a batch "reactor" to allow evaluation of the working principles of the catalytic system and to assess its efficacy toward alkane oxidation. The intent of the present study is not directed toward optimizing the performance of the system for product formation. To accomplish this, a flow system needs to be developed to remove $CH_3OH/H_2O$ continuously with concomitant input of $H_2O_2/H_2O$ to drive the catalytic oxidation. Moreover, for $CH_4$ oxidation, we need to redesign the tricopper complex so that the homogeneous catalyst is functional in a solvent system such as perfluorohydrocarbons with greater solubility for the $CH_4$ gas. Alternatively, the present tricopper catalyst can be encapsulated into the pores of a mesoporous material and the system is converted into a heterogeneous catalyst. These are, however, only technical issues that do not in any way compromise the ideas embodied in this work.

## Acknowledgements

This work is supported by research grants from the National Science Council, Republic of China (NSC 98-2113-M-001-026; 99-2119-M-001-003; 100-2113-M-001-002; and 101-2113-M-001-013- to SIC; and NSC 101–2113M-001–007-MY3 to SSFY). Support from Academia Sinica is also gratefully acknowledged.

## References

1 Inventory of U.S. Greenhouse Gas Emissions and Sinks 1990–2009. USEPA, April 2011.
2 S. Freni, G. Calogero and S. Cavallaro, *J. Power Sour.,* 2000, **87**, 28-38.
3 A. E. Shilov and G. B. Shul'pin, *Chem. Rev*., 1997, **97**, 2879–2932.
4 S. J. Blanksby and G. B. Ellison, *Acc. Chem. Res*., 2003, **36**, 255–263.
5 J. H. Lunsford, *Catalysis Today,* 2000, **63**, 165–174.
6 M. O. Adebajo and R. L. Frost, In *Recent Advances in Catalytic/Biocatalytic Conversion of Greenhouse Methane and Carbon Dioxide to Methanol and Other Oxygenates*, InTech; Europe, 2012; p 338.
7 R. S. Hanson and T. E. Hanson, *Microbiol Rev.,* 1996, **60**, 439–471.
8 S. I. Chan, K. H. C. Chen, S. S.-F. Yu, C. L. Chen and S. S. J. Kuo, *Biochemistry,* 2004, **43**, 4421–4430.
9 S. I. Chan and S. S.-F. Yu, *Acc. Chem. Res.,* 2008, **41**, 969–979.
10 A. L. Feig and S. J. Lippard, *Chem. Rev*., 1994, **94**, 759–805.
11 J. D. Lipscomb, *Annu. Rev. Microbiol.,* 1994, **48**, 371–399.
12 A. C. Rosenzweig, C. A. Frederick, S. J. Lippard and P. Nordlund, *Nature,* 1993, **366**, 537– 543.
13 N. Elango, R. Radhakrishnan, W. A. Froland, B. J. Wallar, C. A. Earhart, J. D. Lipscomb, and D. H. Ohlendorf, *Protein Sci*., 1997, **6**, 556 –568.
14 R. L. Lieberman and A. C. Rosenzweig, *Nature,* 2005, **434**, 177–182.
15 J. B. Vincent, J. C. Huffman, G. Christou, Q. Li, M. A. Nanny, D. N. Hendrickson, R. H. Fong and R. H. Fish, *J. Am. Chem. Soc*., 1988, **110**, 6898 –6900.
16 S. I. Chan, Y. J. Lu, P. Nagababu, S. Maji, M. C. Hung, M. M. Lee, I. J. Hsu, P. D. Minh, J. C. H. Lai, K. Y. Ng, S. Ramalingam, S. S.-F. Yu and M. K. Chan, *Angew. Chem. Int. Ed*., 2013, **52**, 3731–3735.
17 P. P.-Y. Chen, R. B.-G. Yang, J. C.-M. Lee and S. I. Chan, *Proc. Nat. Acad. Sci. USA*, 2007, **104**, 14570–14575.
18 S. I. Chan, C. Y.-C. Chien, C. S.-C. Yu, P. Nagababu, S. Maji and P. P.-Y. Chen, *J. Catal*., 2012, **293**, 186–194.
19 P. Nagababu, S. Maji, M. P. Kumar, P. P.-Y. Chen, S. S.-F. Yu and S. I. Chan, *Adv. Synth. Catal.* 2012, **354**, 3275–3282.



Catalysis of alkane oxidation by a tricopper complex. A tricopper complex can mediate efficient conversion of small alkanes to their corresponding alcohols without over oxidation under ambient conditions.
45x36mm (300 x 300 DPI)