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Methane hydroxylation: a biomimetic approach

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Contents

I.	Introduction	291
II.	Methane activation with metal complexes	292
III.	Activation of O_2. Iron-based catalysts and systems	297
IV.	Copper-based catalysts	304
V.	Gold catalysis	308
VI.	Conclusions	310

Abstract. The review addresses direct methane oxidation — an important fundamental problem, which has attracted much attention of researchers in recent years. Analysis of the available results on biomimetic and bio-inspired methane oxygenation has demonstrated that assimilating of the experience of Nature on oxidation of methane and other alkanes significantly enriches the arsenal of chemistry and can radically change the character of the entire chemical production, as well as enables the solution of many material, energetic and environmental problems. The bibliography includes 310 references.

I. Introduction

Huge methane reserves on Earth and its permanent reproduction as a result of the global circulation of carbon ($\sim 10^9$ metric tons per year),[1] as well as the energy, material and environmental needs of mankind, on the one hand, and the extraordinary inertness of the CH_4 molecule, on the other hand, pose a fundamental challenge to chemistry as to how to activate methane thus enabling rational use of this valuable raw material. In addition to conventional deposits of natural gas containing methane as a major component, immense reserves of methane hydrates are hidden in the bowels of the Earth. These reserves are roughly estimated at $(1-1.5)\times 10^{13}$ tons (as recalculated to carbon), *i.e.*, $\sim 50\%$ of all carbon on the Earth.[1] Because of the lack of efficient processes of converting methane to methanol and other chemical compounds, natural gas is used exclusively as fuel. However, even as fuel, natural gas is somewhat inconvenient since its transportation and storage present difficulties. At the same time, methane is an ideal feedstock for the chemical industry since it can be converted to any organic compounds (polymers, dyes, drugs, *etc.*); however, efficient catalysts capable of realizing these transformations without significant energy inputs as low-stage processes are still unknown. Among a great number of publications dealing with this problem, noteworthy is the paper by Lunsford[2] characteristically entitled 'Catalytic conversion of methane to more useful chemicals and fuels: a challenge for the 21st century'.

Methanol — a product of methane hydroxylation (oxygenation, functionalization, oxidation) — is a more convenient source of stored energy than methane and a more valuable feedstock for the chemical industry.[3] Methanol is among the most significant large-scale products of the chemical industry. It is used as a semi-product in various chemical productions, and is an excellent fuel for different engines, including internal combustion engines. Whereas total annual natural gas production is about 3000 million tons, approximately 30 million tons of methanol per year is produced worldwide; *i.e.*, chemical conversion of methane, including other methods for its processing, accounts for only 1% – 2% of produced methane. At the same time, methanol demand will inevitably increase.

A modern method of methanol production involves high-temperature conversion of methane to syngas ($CO + H_2$), which is then catalytically converted to CH_3OH and other products. This method is continuously improved; but it becomes more and more unable to meet the growing economic and environmental demands since it occurs at high temperatures and pressures and, above all, leads to by-products. In this context, the search for ways of how to oxidize methane directly to methanol becomes increasingly important.[4 – 6] Whereas the industrial method of producing methanol is a high-temperature and multistep process, as many as $\sim 6\times 10^8$ tons of methane are annually oxidized by aerobic bacteria in nature. Microorganisms use methane as the only carbon and energy source and convert

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it directly to methanol under mild physiological conditions. This evidence strongly suggests that such a process is, in principle, possible.

Chemical treatment of methane requires its functionalization.[7,8] The most acceptable method of methane functionalization, from both the economical and environmental points of view, is its catalytic oxidation with dioxygen. Methane, the simplest member of alkanes or paraffin hydrocarbons (from the Latin *parum affinis*, meaning little affinity), is the most inert among them. Under common conditions, an oxygen molecule is also rather inert, which is essential for sustaining life of Earth. Whereas radical reactions involving hydrogen atom abstraction are most typical of alkanes, only the most active species, for example, $HO^{\bullet}$ and $MeO^{\bullet}$ radicals or the $^{\bullet}O^{\bullet}$ atom, can abstract an H atom from methane, which has the strongest C–H bond (the dissociation energy is 105 kcal mol^{-1}).[9] The uncontrollable development of processes involving these radicals leads to combustion or explosion owing to the propagation of chain reactions.

Available processes of controlled incomplete oxidation of methane are, as a rule, high-temperature and insufficiently selective.[10] Inasmuch as the elementary event of the methane reaction with dioxygen is very slow under common conditions, direct selective oxidation of methane at low temperatures requires activation of methane or dioxygen or both these molecules.

Alkane activation by metal complexes was discovered more than 40 years ago when studying the deuterium–hydrogen exchange of methane in aqueous acetic acid solutions of platinum(II) complexes.[11] Later, methane activation was revealed in the presence of other transition metal complexes (Pd, Ir, Rh, Hg, Au and others) and for other alkanes. Nowadays, this is a large rapidly developing area of chemistry.

It turned out that, under anaerobic conditions, Nature also follows the same path of methane functionalization. According to estimates,[1] $\sim 3 \times 10^8$ tons of methane are annually oxidized by anaerobic bacteria using Mn^{IV} and Fe^{III} compounds or anions (sulfate, nitrate, nitrite) as terminal acceptors instead of O_2. The homogeneous activation of methane in solutions of transition metal complexes is a chemical model of anaerobic methane oxidation in nature. In last years, efficient metal-based systems have been revealed for methane activation and oxidation to methanol with a conversion of up to 90% and selectivity of up to 80%. However, drawbacks of such systems are the necessity of hydrolyzing the initially forming methanol esters and relatively severe reaction conditions. At the same time, activation of dioxygen by metal-containing oxygenases makes it possible to carry out the direct conversion of methane to methanol under considerably milder conditions and with higher efficiency and selectivity.

The occurrence of the aerobic low-temperature selective process of enzymatic oxidation of methane to methanol in nature challenges researchers to answer some difficult questions. How can such a strong molecule be oxidized without activation at room temperature and ambient pressure to give the only product? What must be the nature of an active species capable of abstracting an H atom from methane and concurrently compatible with the protein environment? How is the high selectivity of the process achieved or, in other words, how can the inert methane be oxidized without subsequent oxidation of the more reactive methanol?

By the end of the 20th century, the structure of the active site and the mechanism of functioning of the major class of oxygenases, the cytochrome P450 family (mononuclear haem iron enzymes), have been roughly determined, and the prominent role of an iron atom in the biological activation of O_2 has been demonstrated.[12] At the same time, studies of other classes of iron oxygenases have been initiated. Copper-containing oxygenases have also been discovered. In recent years, significant progress has been achieved in understanding the mechanism of biological oxidation of the unactivated C–H bond by oxygenases. However, many details of these reactions, especially those involving methane monooxygenases (MMOs), are still unclear. No efficient chemical models of MMOs have been developed so far. On the one hand, it has been recognized that MMOs are highly organized multicomponent enzymatic systems; on the other hand, the evolution of MMOs had to begin from simpler systems that would be rather efficient to be assimilated by the organisms. This idea stimulated the search for simple MMO models.

MMO is a binuclear iron or copper biocomplex, which catalyzes, under mild conditions, oxygenation of methane, the simplest and least reactive saturated hydrocarbon:

$$CH_4 + O_2 + NADH + H^+ \longrightarrow CH_3OH + H_2O + NAD^+,$$

NADH is nicotinamide adenine nucleotide.

This unique reaction has captivated the imagination of many researchers in the past 20 years. If we could design a commercial biomimetic catalyst mimicking the reactivity of MMO, large-scale conversion of methane to methanol would significantly increase its use as a low-cost energy source and feedstock for diverse industrial processes.

Although these questions have been repeatedly addressed in numerous reviews of the literature, our task was to systematically consider the entire body of information on the conversion of methane to methanol from the viewpoint of the biomimetic or, more generally, bio-inspired approach.

The present review comprises four sections where we consider biological and biomimetic catalysts based on platinum group metals, iron, copper and gold. Our major focus is on methane oxygenation mechanisms and the nature of the resulting metal–oxygen intermediates. The activation of methane in metal complex solutions is considered only briefly since this problem has been covered in detail in reviews and monographs (see Section II.2).

II. Methane activation with metal complexes

1. Anaerobic oxidation of methane in nature

Anaerobic oxidation of methane is one of the most debatable and still inadequately studied areas of chemistry.[13] It has long been believed that methane is inert under anaerobic conditions and can be assimilated only by aerobic microorganisms. The first evidence of anaerobic oxidation of methane, taken with a large grain of salt, has appeared by the mid-1960s, but only in the last decade, convincing proof of the existence of such a process has been obtained.[14]

By now, microorganisms capable of utilizing methane for their vital functions in the absence of O_2 have been characterized.[13,15] Indeed, in the global carbon circulation, we can distinguish the methane cycle, which involves both

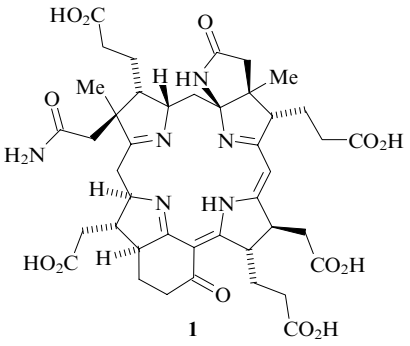
methane-producing bacteria (methanogens) and methane-consuming bacteria (methanotrophs).[14,15] As mentioned above, anaerobic methanotrophs use sulfate, nitrate or nitrite anions, as well as Mn^{IV} or Fe^{III} ions, as terminal acceptors instead of O_2. The process involving the sulfate is most commonly encountered owing to the accessibility of the anion; however, thermodynamically it is not the most favourable process ($\Delta G^{\circ\prime}$ is the change in the standard Gibbs energy):[16]

$$CH_4 + SO_4^{2-} + H^+ \longrightarrow CO_2 + HS^- + 2\,H_2O \qquad (1)$$

($\Delta G^{\circ\prime} = -21$ kJ mol^{-1}).

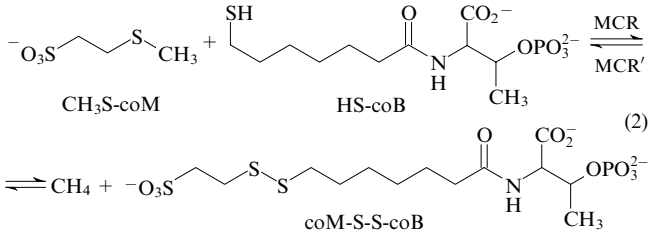
At present, at least two different mechanisms of anaerobic methane oxidation are discussed. One of them involves the key nickel enzyme of methanogenesis, namely, methyl-coenzyme M reductase (MCR).[17] The other mechanism has been recently discovered in N_2-forming methanotrophs[18] and it unexpectedly involves the copper monooxygenase enzyme of aerobes, pMMO (see Section IV.1).

For sulfate methanotrophs, it has been proved that methane is activated by the nickel complex with the tetrapyrrole macrocyclic ligand corphin (**1**), so-called factor F430, which is the prosthetic group of the key nickel enzyme MCR.[17]



1

In methanogenic organisms, MCR catalyses the final and rate-limiting stage of methane biogenesis [reaction (2), $\Delta G^{\circ\prime} = -30 \pm 10$ kJ mol^{-1}]: the reduction of methyl-coenzyme M [2-(methylthio)ethanesulfonate, CH_3S-coM] by coenzyme B (7-mercaptoheptanoylthreonine phosphate, HS-coB) to CH_4 and heterodisulfide (coM-S-S-coB).



(2)

All available data suggest that the sulfate-driven anaerobic methane oxidation is reverse methanogenesis ($\Delta G^{\circ\prime} = 30 \pm 10$ kJ mol^{-1}) using an MCR homologue, the MCR′ enzyme [see reaction (2)] to catalyze methane activation.[16,19–21] In order to be functionally active, the Ni atom in MCR should be in the oxidation state +1.[22] However, the Ni^{I}F430 complex is very unstable and readily converts into Ni^{II}F430 even in the absence of O_2. Studies of the crystal structure of MCR′ showed that the nickel(II) complex with an analogue of ligand **1** is buried deep in the protein and is connected with the surface through a hydrophobic channel 50 Å in length, which presumably serves to transport methane and sulfide coenzymes.[23] One of the axial positions of Ni^{II}F430 is occupied by the carboxamidate ligand while the other axial position is vacant and capable of binding to substrates.

It turned out that the MCR itself, isolated from methanogens and purified, is able to catalyze methane oxidation to methyl-coenzyme M.[17] The kinetic characteristics of this process are consistent with the values estimated for cultures catalyzing anaerobic methane oxidation. Although the mechanism of anaerobic methane oxidation with activation on a nickel complex has been suggested previously,[24] this is the first experimental observation of methane activation by an anaerobic enzyme without the participation of an active metal–oxygen intermediate and, hence, the first proof of metal complex methane activation in living systems.

In 2006, it was reported for the first time that a microbial consortium uses methane and nitrite for nutrition under strictly anaerobic conditions.[25] In this microbial consortium, the endergonic process of anaerobic methane oxidation was coupled to the exergonic reduction of nitrite to dinitrogen:

$$3\,CH_4 + 8\,NO_2^- + 8\,H^+ \longrightarrow 3\,CO_2 + 4\,N_2 + 10\,H_2O \qquad (3)$$

($\Delta G^{\circ\prime} = -928$ kJ mol^{-1} CH_4).

Since, according to isotopic studies, an oxygen atom from NO_2^- was revealed in the methane oxidation products, the authors suggested that the microorganism can catalyze the conversion of two NO molecules to N_2 and O_2 and that the anaerobically generated oxygen is used for methane oxidation to methanol by aerobic copper-containing oxygenase. However, the moiety that catalyzes the dismutation of 2 NO to N_2 was not identified in this microorganism, and no bacteria were grown when NO_2^- was replaced by dioxygen. Therefore, it cannot be ruled out that copper-containing oxygenase in the anaerobic methanotroph can catalyze methane oxidation directly by nitrogen dioxide, without its conversion to O_2.[26]

In this context, it should be noted that copper-containing zeolites catalyze processes of NO destruction.[27] The participation of O_2 in an anaerobic process seems to be almost improbable and, although it can be assumed in the case of nitrite, is absolutely impossible for microorganisms that use sulfate in which methanol can be excluded as a primary product on thermodynamic grounds.[16] At the same time, the functional activity of MCR in the Ni^{I}F430 form, the low redox potential of the Ni^{II}F430/Ni^{I}F430 pair ($E^{\circ\prime} \leqslant -0.6$ V) and, just the reverse, relatively high redox potentials of the NO_3^-/NO_2^- ($E^{\circ\prime} = +0.43$ V), NO_2^-/NO ($E^{\circ\prime} = +0.34$ V), NO_2^-/N_2O ($E^{\circ\prime} = +1.17$ V) and N_2O/N_2 ($E^{\circ\prime} = +1.36$ V) pairs make it evident that the use of this enzyme by denitrifying methanotrophs is fundamentally impossible.

Recently, it has been demonstrated that Mn^{IV} or Fe^{III} compounds can also be terminal oxidants in anaerobic methane oxidation.[28] These processes can be described by the following equations of complete oxidation (ΔG is the change in the Gibbs energy under the experimental conditions[28]):

$$CH_4 + 4\,MnO_2 + 7\,H^+ \longrightarrow HCO_3^- + 4\,Mn^{2+} + 5\,H_2O \quad (4)$$

($\Delta G = -556$ kJ mol^{-1}),

$$CH_4 + 8\,Fe(OH)_3 + 15\,H^+ \longrightarrow HCO_3^- + 8\,Fe^{2+} + 21\,H_2O \quad (5)$$

($\Delta G = -270$ kJ mol^{-1}).

Although the rates (w_n) of these processes are lower than the rate of the sulfate methanotroph reaction

$$CH_4 + SO_4^{2-} \longrightarrow HCO_3^- + HS^- + H_2O \quad (6)$$

($\Delta G = -14$ kJ mol^{-1})

($w_6 : w_4 : w_5 = 26 : 7 : 3$), comparison of Eqns (4)–(6) shows that the amount of the produced energy is much higher. Inasmuch as Mn^{IV} ($E^{\circ\prime} = +0.41$ V) or Fe^{III} ($E^{\circ\prime} = +0.2$ V) is incompatible with the Ni^{I}F430 complex (see above) and nitrogen oxides are absent (as in the case of denitrifying methanotrophs), the nature of methane-activating sites for Mn^{IV} or Fe^{III} as a terminal oxidant remains a mystery. These oxidants *per se* are also unable to abstract a hydrogen atom directly from methane, for which $E^{\circ\prime}(CH_3^{\bullet}/CH_4) = +2.1$ V.

The mechanism of anaerobic methane oxidation has been best studied for sulfate methanotrophs; however, in this case as well, the methane activation at the nickel site has been inadequately understood. The intermediate formation of the methyl derivative of the NiF430 complex (CH_3-NiF430) has been suggested in some works,[29,30] but denied in other works (see, *e.g.*,[31]). However, such an intermediate was never experimentally observed in methanogenesis because of its instability under these conditions. The stable CH_3-Ni^{III}F430 complex can be artificially obtained by treating the Ni^{I} enzyme form with methyl iodide,[32,33] and when HS-coM is added, the complex undergoes conversion to methylated coenzyme,[32] which seems to confirm its participation in catalysis. The geometric and electronic structures of CH_3-Ni^{III}F430 in solution have been characterized by X-ray absorption spectroscopy (XAS) and calculated by the density functional theory (DFT) method,[34] and its crystal structure has been determined by X-ray crystallography.[35]

Different mechanisms of methane oxidation by the enzyme systems of sulfate methanotrophs have been considered in the literature.[16,22] Several schemes have been suggested. One of the most probable schemes is believed to be electrophilic metallation of methane in its reaction with the high-valence Ni^{III} complex of MCR.[16] Since free Ni^{III}F430 is a strong electrophile, this scheme is similar to electrophilic activation of alkanes by high-valence transition metal complexes (see Section II.2). However, according to DFT calculations, the formation of CH_3-NiF430 in the reaction of $Ni^{II(III)}$F430 with methane is thermodynamically impossible.[31] At the same time, multiple isotope exchange with a deuterated medium observed upon the reaction of purified MCR with CH_3S-coM and HS-coB in both the forming methane and the remaining CH_3S-coM not only confirms the reversibility of this reaction but also demonstrates the participation of the σ-CH_4 intermediate in the process (see Section II.2).[36]

How can all these results be reconciled? For highly organized active sites of natural catalysts and taking into account the propensity of the C–H bond for homolytic reactions, we believe that a more probable mechanism is the mechanism similar to the methane activation on radical-like Rh^{I} complexes

$$[Rh^{I}\cdots H-CH_3\cdots Rh^{I}] \longrightarrow [Rh^{II}-H + CH_3-Rh^{II}] \quad (7)$$

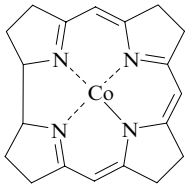
represented by the following sequence of reactions:

$$[coM\text{-}S^{\bullet}\cdots H-CH_3\cdots Ni^{I}] \longrightarrow [HS\text{-}coM + CH_3-Ni^{II}], \quad (8)$$

$$[HS\text{-}coM + {}^{\bullet}S\text{-}coB] \longrightarrow [{}^{\bullet}S\text{-}coM + HS\text{-}coB],$$

$$[CH_3-Ni^{II} + {}^{\bullet}S\text{-}coM] \longrightarrow [CH_3S\text{-}coM + Ni^{I}].$$

The structure of the MCR active site demonstrates that the methane formation and oxidation reactions occur in a hydrophobic 'pocket'. Methane enters and exits through a hydrophobic channel, and this channel also serves to transport hydrophobic hydrosulfides (HS-coB and HS-coM) and the coB-S-S-coM heterodisulfide. It has been shown that coenzyme B induces coordination of coenzyme M to Ni^{I}F430 through the sulfur atom in active MCR, which, in turn, leads to conformational changes on the active site.[37] For functionalization of unactivated C–H bonds in the absence of O_2, Nature widely uses 5′-deoxyadenosyl radical (5′dA$^{\bullet}$, $E^{\circ\prime} = +1.4$ V) as the active oxidant. The precursor of this radical is 5′-deoxyadenosylcobalamin, vitamin B_{12} coenzyme, which contains cobalt corrin tetrapyrrole complex (Co^{III}K, **2**).



2

Binding to the substrate induces Co–C bond homolysis generating 5′dA$^{\bullet}$ and Co^{II}K. A similar process could also occur in the case of the Ni^{II}–S-coM complex. In addition to 5′dA$^{\bullet}$, other radicals are generated, including thiyl radicals (RS$^{\bullet}$), for activation of C–H bonds with a strength of up to 98 kcal mol^{-1} under anaerobic conditions.[38] Thus, concurrent binding of the $^{\bullet}CH_3$ radical to Ni^{I} would enable the cleavage of the strong C–H bond in methane by the thiyl radical.

2. Methane oxidation in solutions of transition metal complexes

Homogeneous activation of methane in solutions of transition metal complexes is a chemical model of anaerobic methane oxidation in nature. Methane activation is only part of the vast and rapidly developing field of investigation of metal complex activation of hydrocarbons, which has been well covered in a number of excellent reviews and books.[39–54] In early works dealing with the alkane activation problem,[11,55,56] important observations have been made and hypotheses serving as a basis for its further development have been suggested.

In 1969, first observations of the H/D exchange in methane and ethane in solutions of Pt^{II} chloride complexes in a D_2O–CD_3CO_2D mixture at 100 °C were reported.[57] Study of multiple exchange, *i.e.*, concurrent formation of CH_3D, CH_2D_2, CHD_3 and CD_4, led to the conclusion that intermediates with $Pt-CH_3$, $Pt{=}CH_2$, $Pt\cdots CH_4$ and $H-Pt-CH_3$ fragments were involved in exchange.[58,59]

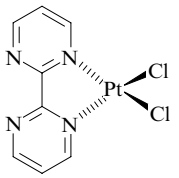
Later, the formation of $Pt-CH_3$ was proved by methylation of Pt^{II} complexes by organomercury compounds, then by NMR and, finally, by isolation of MePtCl from the reaction of Pt^{II} chloride complexes with methane.[60–62] The Pt^{II}-activated methane could be further converted to functional derivatives (CH_3Cl, CH_3OH) in catalytic processes with the use of different terminal oxidants: $[PtCl_6]^{2-}$, quinones, polyoxometalates (heteropoly acids), $CuCl_2$ and O_2.[63–65]

An important characteristic of metal complex activation of methane revealed in early works[47,63] is extraordinary bond selectivity. Whereas the rate of radical reactions depends on the strength of the broken C–H bond (tertiary > secondary > primary), metal complex activation of this bond is usually more preferable for the less sterically crowded terminal methyl group, *i.e.*, it follows the reverse order of selectivity. The Pd^{II} complexes in trifluoroacetic or sulfuric acid are also able to activate and oxidize C–H bonds of alkanes.[66–68] Although platinum complexes have been best studied by now in the context of methane activation and functionalization, the range of other transition metals is rapidly extended.

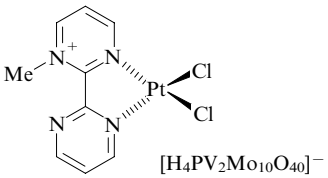
Methane activation by platinum salts can also occur in neat water; however, such a system is unstable: the reduction of Pt^{II} by methane leads to precipitation of platinum metal. Acids (acetic, trifluoroacetic and sulfuric) stabilize this system. Better stabilization is achieved by using ligands; however, this entails a decrease in activity in the series $H_2O > Cl^- >$ pyridine (Py) > PPh_3.[69] A compromise between stability and activity is achieved for middle members of the series, Cl^- and Py. An important factor is the stability of ligands and their complexes to corrosive acidic and oxidative media.

Another problem of selective oxidation of methane to methanol is that methanol itself is more reactive than methane and is oxidized further. In strong acids, like sulfuric and trifluoroacetic, methanol is converted to esters of these acids, which are more stable to further oxidation, are easily isolated and can then be hydrolyzed to methanol. In particular, the reactivities of methane, methanol and methyl sulfate are related to each other approximately as 100 : 1000 : 1.[41] Based on this fact, efficient and highly selective systems for methane oxidation have been designed (Table 1).

As follows from Table 1, the most efficient system suitable for large-scale use is system No. 1 based on the platinum bipyrimidine complex $[PtCl_2(bipim)]$ (**3**).



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At a rather high conversion (90%), the high selectivity (80%) is retained since further oxidation of the forming methanol is prevented by its conversion to methyl bisulfate. The latter is hydrolyzed to regenerate the target product,

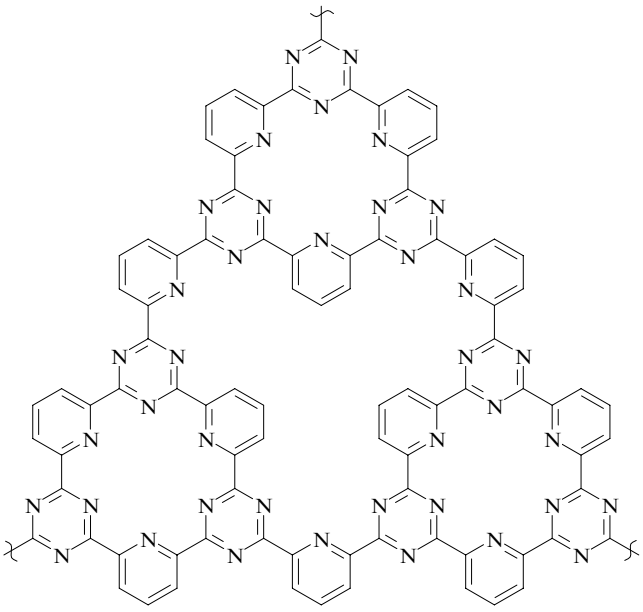
Table 1. Activation and selective oxidation of methane to CH_3X catalyzed by platinum group metal and gold complexes.

System, No.	Catalyst	Terminal oxidant	Medium	T/°C	Conversion (%)	X	Selectivity (%)	TON [a]	TOF [b]/h^{-1}	Ref.
1	$[PtCl_2(bipim)]$ (**3**)	SO_3	30% oleum	220	90	OSO_3H	81	500	36	70
2	$[PtCl_2(Me\text{-}bipim)]^+$ $[H_4PV_2Mo_{10}O_{40}]^-$ (**4**)/SiO_2	$H_5PV_2Mo_{10}O_{40}/O_2$	H_2O	50	1	OH	50	33	8	71
3	$[Pt^{II}(CTF)]$ (Pt-**5**)	SO_3	30% oleum	215	–	OSO_3H	75	300	100	72
4	[Pd(NHC)] (**6**)	$K_2S_2O_8$	CF_3CO_2H, $(CF_3CO)_2O$,	90	4	O_2CCF_3	100	30	2	73
5	$[Pd(OAc)_2]$	$NaNO_2/BQ/O_2$	CF_3CO_2H	80	–	O_2CCF_3	100	7	1	74
6	$[Pd(OAc)_2]$	$H_5PV_2Mo_{10}O_{40}/BQ/O_2$	CF_3CO_2H, n-C_8F_{18}	80	–	O_2CCF_3	90	120	15	75
7	$[Ir(NNC)](O_2CCF_3)_2$ (**7**)	$NaIO_4$	CF_3CO_2D	180 105	5	O_2CCF_3	100	6 62	2 2	76
8	$Au(Au^{I,III})$	H_2SeO_4	96% H_2SO_4	180	28	OSO_3H	90	30	4	77
9	$Au^{0,I}/SiO_2$	$K_2S_2O_8$	[Bmim]Cl, CF_3CO_2H, $(CF_3CO)_2O$	90	20	O_2CCF_3	72	18	1	78
10	Au^IL [c]	$K_3[Fe(CN)_6]$	H_2O	25	10	OH	100	35	18	see [d]

Note. The following abbreviations and acronyms are used: bipim is 2,2′-bipyrimidine, Me-bipim is *N*-methyl-2,2′-bipyrimidinium, CTF is polymeric ligand **5**, NHC is N-heterocyclic dicarbene, BQ is *p*-benzoquinone, NNC is *ortho*-C-deprotonated 4,4′-di-*tert*-butyl-6-phenyl-2,2′-bipyridine, [Bmim]Cl is 1-benzyl-3-methylimidazolium chloride. [a] TON (turnover number) = $[CH_3X]/[Cat]$; [b] TOF (turnover frequency) is TON per unit time; [c] L is rutin or quercetin (see Section V); [d] A F Shestakov, A K Shilova, A P Sadkov, N V Larionova, S A Golovanova, L A Levchenko, A E Shilov *Dokl. Chem. (Engl. Transl.)* (2012) (in the press).

methanol. This system was approved by the Catalytica Company (United States) in the pilot project; however, its commercial use is hindered by the difficulty of separation and regeneration of the catalyst. An analogous ligand is used in complex **4**.

A better candidate is presumably system No. 3, which involves the heterogenized Pt^{II} complex with a polymeric ligand, covalent triazine-based framework (CTF, **5**) containing the triazine framework with pyridyl groups for extra coordination to the metal.[72]

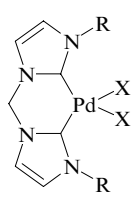


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An advantage of such a system is that the catalyst can be easily separated from the reaction mixture by simple filtration and is rather stable under catalysis conditions so that it can be recycled several times without significant loss of activity. In addition, this system shows the highest rate of catalytic methane oxygenation (TOF = 100 h^{-1}!). However, the use of systems Nos 1 and 3 is complicated by a rather corrosive medium and relatively high temperatures.

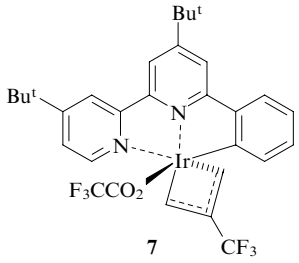
Systems Nos 2, 4, 5, 6 and 9 are closer to 'green chemistry'. Especially remarkable in this respect is system No. 2, which operates at rather low temperature (50 °C) and uses an aqueous solution as a medium and oxygen or air as an oxidant. However, in addition to methanol, this system produces formaldehyde and acetaldehyde, which decreases the selectivity to methanol to 50%. The unexpected formation of acetaldehyde in this process is attributed [71] to the reaction of formaldehyde with the activated methane molecule in the platinum coordination sphere.

Good results have also been obtained with the use of systems Nos 4 and 7, based on palladium and iridium complexes with heterocyclic ligands (**6** and **7**, respectively).



6

R = Me, Bu^t; X = Cl, Br.

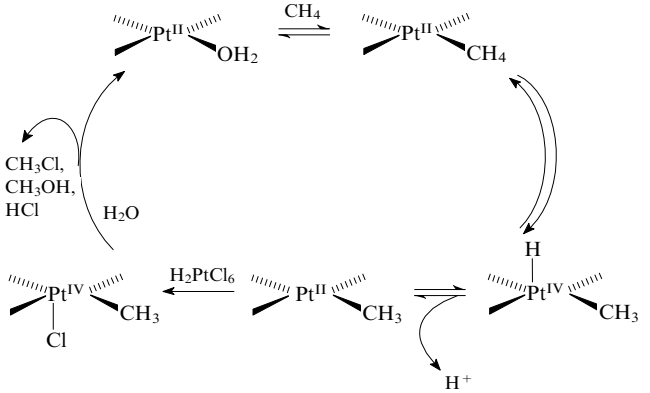


7

System No. 9, owing to the use of an ionic liquid as a medium, is characterized by enhanced stability; however, its efficiency is still low. It is likely that the most promising system is recently discovered system No. 10, which operates in water at room temperature. As distinct from similar system No. 2, system No. 10 affords 100% selectivity to methanol and, thus, is the best functional model of anaerobic methane oxidation.

Studying the kinetics of activation and oxidation of methane and other C–H compounds by platinum complexes allowed one to suggest the nature of the interaction of alkanes with Pt^{II} and the mechanism of this reaction (Scheme 1).[11, 55, 56]

Scheme 1



As shown by this scheme, initial interaction of methane with the metal atom in the complex leads to the activation of the CH_4 molecule and is followed by formation of the intermediate methyl complex $Pt^{II}-CH_3$, which is considerably more reactive than methane. In the presence of oxidants, such an intermediate undergoes mild oxidation at ~100 °C to methanol, among other compounds. These ideas have been confirmed and developed in further experimental studies and quantum chemical calculations.[51, 76, 79–83] Based on calculations, new catalysts of methane oxidation have been proposed, namely, the $Pt^{II}-CF_3CO_2H$ [76] and $Au-H_2SO_4$ systems.[77] According to modern concepts (see Scheme 1), the mechanism of methane activation by transition metal complexes involves several stages. At the first step, the methane molecule enters the metal coordination sphere to form the $M \cdot CH_4$ σ-complex (M is a metal). Early proofs for the formation of similar complexes was not only the observation of multiple deuterium exchange (see above) but also the occurrence of the reverse isotope effect in the elimination reactions of alkyl hydride complexes.[41] Density functional theory calculations confirmed that Pt^{IV} methyhydride complex formed in the second stage spontaneously releases H^+ to the solution bulk.[79]

Recently, the first methane σ-complex was obtained by protonation of the Rh^I-CH_3 complex in a $CDFCl_2$ solution at −110 °C. It has been comprehensively characterized by NMR [84] since it has a rather long lifetime under these conditions. Calculations have predicted that the σ-complex in this system is more stable than the methyl hydride complex being at equilibrium with it, as follows from ^1H NMR data. According to calculations, in such a complex only one C–H bond of methane is coordinated to the metal (Fig. 1), although there is equilibrium between η^2-C,H and η^2-H,H conformers, which is strongly shifted to the left.

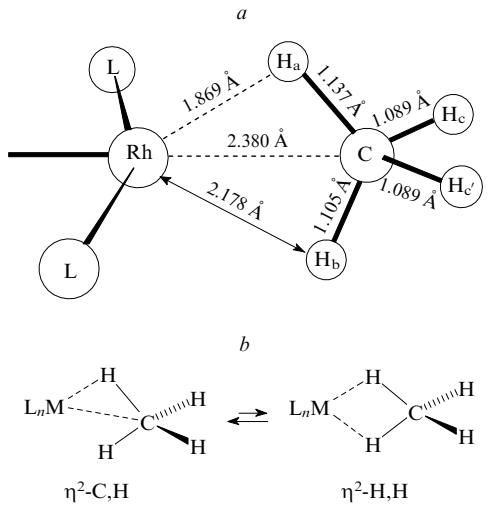


Figure 1. Rh^{I} methane complex (*a*) and its possible conformations (*b*) (L is a ligand).[84]

It is worth noting that the $Rh^{I}\cdot CH_4$ σ-complex is isoelectronic with the $Pt^{II}\cdot CH_4$ σ-complex assumed to form in methane reactions with Pt^{II} compounds. The existence of the kinetic isotope effect (KIE) in these reactions shows that the rate-limiting stage is C–H bond cleavage with formation of the methyl hydride intermediate. Correlation of the rate constants (k) of the H/D exchange in H–CXYZ compounds (X, Y, Z = H, Cl, F, CH_3, CF_3, OH, CO_2H, Ph) has been performed with the use of the two-parameter Taft equation[85] for radical H atom abstraction:

$$\log(k/k_o) = \rho^*\sigma^* + n\psi,$$

where k_o is the H/D exchange rate constant in methane, ρ^* is the reaction parameter, σ^* is the electronic parameter of a substituent, n is the number of substituents, and ψ is the parameter of conjugation between the substituent and the reaction site. It has been demonstrated that Pt^{II} exhibits only moderate acceptor properties ($\rho^* = -1.4$), and the C–H bond cleavage in the elementary event of Pt^{II} insertion into it occurs by the homolytic mechanism.[86] For the recently isolated and characterized stable Ir^{III} methyl hydride complex (the half-life time is $t_{1/2}$ = 3 h at 23 °C),[87] rapid proton exchange between Ir–H and Ir–CH_3 has been revealed. Calculations show[87,88] that the $Ir^{III}\cdot CH_4$ complex in this case is only 5 kcal mol^{-1} higher on the energy scale than the ground state of the H–Ir–CH_3 species.

In all of the above examples, C–H bond activation and cleavage occur as a two-electron process at one metal atom. However, this bond cleavage can occur by the concerted mechanism involving two radical-like species, as, for example, in the case of rhodium porphyrin (Rh^{II}Por) being at equilibrium with its dimer. The sequence of transformations can be represented in the following way:

$$(Rh^{II}Por)_2 \longrightarrow 2\,Rh^{II}Por + CH_4 \longrightarrow \quad (9)$$
$$\longrightarrow [PorRh^{II}\cdots H-CH_3\cdots Rh^{II}Por] \longrightarrow$$
$$\longrightarrow H-Rh^{III}Por + CH_3-Rh^{III}Por.$$

Since the porphyrin ligand creates strong steric hindrances to the approach of the alkane to the rhodium atom, methane turns out to be the most active agent in this reaction.[89] Under laboratory conditions, isotope exchange between methane and D_2 was observed in the reaction catalyzed by the bis(cyclopentadienyl)hydride complex of Ni^{II}, the metal that also 'operates' in nature. This result points to the possibility of formation of the $Ni^{II}-CH_3$ complex and, hence, to the ability of the intermediate Ni^{I} complex to activate methane.[90]

III. Activation of O_2. Iron-based catalysts and systems

1. Soluble methane monooxygenase

Aerobic methanotrophic bacteria oxidize methane to methanol at the first stage of its metabolism by means of the methane monooxygenase enzyme. This enzyme exists in two forms: the less abundant but well studied multicomponent soluble form (sMMO)[91–98] and the hardly isolable and, thus, insufficiently studied copper-containing membrane-bound form (pMMO, see Section IV). Among the iron-containing MMOs, the sMMOs isolated from two microorganisms, *Methylococcus capsulatus Bath* (*Mc*) and *Methylosinus trichosporium OB3b* (*Mt*), have been studied in most detail. There are slight differences between these oxygenases.[97]

Oxygenase sMMO shows a wide range of substrate specificity and, in addition to methane, it is able to oxygenate more than 50 compounds, including linear alkanes up to n-octane (at the terminal methyl group and the neighbouring methylene group), cyclic and aromatic hydrocarbons (hydroxylation) and alkenes (epoxidation or dihydroxylation). It reacts with higher hydrocarbons more slowly than with methane notwithstanding the fact that the C–H bond in them is weaker than in methane. In branched alkanes, the part of the molecule most distant from the branching site is oxidized. This suggests that the decisive factor in reactions involving sMMO is steric hindrance rather than the strength of the attacked bond.

The hydroxylase component of sMMO (**H**)[99,100] is an $(\alpha\beta\gamma)_2$ dimer composed of two sets of α, β and γ subunits. In the polyenzyme complex, this component functions together with reductase and small coupling (regulatory) protein B, which is of paramount importance for catalysis. The active site containing the Fe_2 cluster is located in the α subunit. Kinetic data indicate that the interactions of all three sMMO components are important for catalysis: these components have a high affinity for each other and form the polyenzyme complex in which the Fe_2 cluster is capable of two-electron reduction. Protein B regulates electron transfer from reductase to hydroxylase so that this transfer occurs only in the presence of substrates; it also promotes alkane oxidation and changes its regioselectivity. It is believed that protein B controls access of the substrate to the active site,[101–104] opening or expanding the hydrophobic channel through which the substrate is delivered to the active site; *i.e.*, protein B acts like a molecular sieve.

The active site in sMMO[99,105,106] contains the binuclear iron biocomplex in which the iron atoms are bound to the protein through four glutamate residues (Glu) and two histidine residues (His) (designated by, respectively, letters E and H in Fig. 2). In the course of the catalytic cycle, one of the carboxylate groups is retained as the bridge between

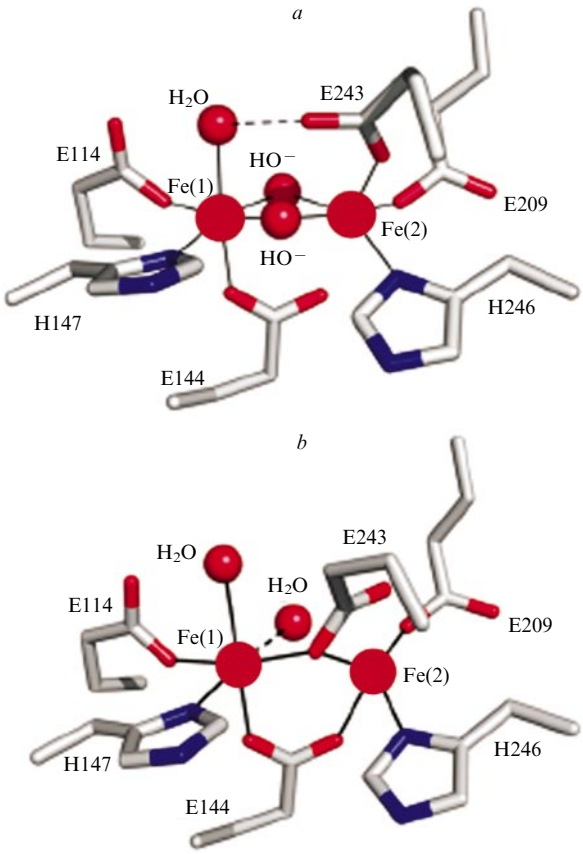


Figure 2. Active site of the sMMO in the oxidized (ferri) (*a*) and reduced (ferro) (*b*) states.[97]

the iron atoms, which is presumably important for their coupled functioning. In addition, the iron atoms can be bonded to several exogenous hydroxide or aqua ligands, some of which, together with the carboxylate group, form three bridges between the iron atoms at most. As distinct from the haem iron in cytochrome P450, which has only one coordination site for formation of oxygen-containing intermediates, there are four inner coordination sites in MMO, occupied in the resting ferri state by two bridging OH groups,[92, 107, 108] that can be involved in the catalytic process at the stage of reductive O_2 activation. Electrons for this process are transferred from NADH by an other enzyme, reductase.

The active site also contains a hydrophobic substrate-binding cavity of about 185 Å^3 in volume, bounded by the binuclear iron complex on one side and lined with hydrophobic amino acid residues of protein on the opposite side.[99, 106, 107] Substrate binding in this hydrophobic pocket initiates rapid two-electron reduction of the iron(III) cluster to iron(II).[100]

By 2001, 34 structures of different sMMO forms (ferri and ferro) had been determined by X-ray crystallography, which provided reliable information of the structural details of the active site of sMMO in the oxidized and reduced states.[91] These structures differ in conformation, which can play an important role in different steps of the catalytic process. Crystallographic studies also revealed several adjacent hydrophobic cavities in the α subunit that determine the path of CH_4 and O_2 to the binuclear site.[98]

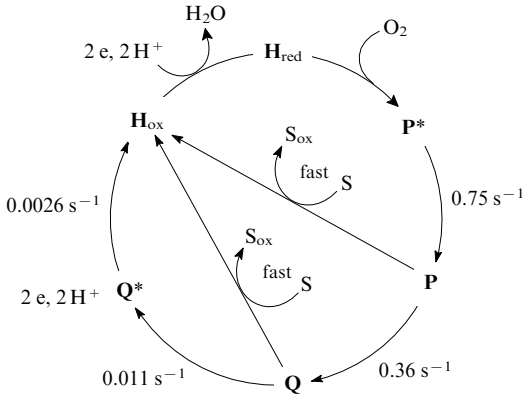
In oxidized sMMO (Fig. 2 *a*), both iron atoms are in a distorted octahedral environment and are not equivalent. The distance between them is ~3.1 Å. The Fe(1) atom has a terminally coordinated water molecule. The coordination environment of the Fe(2) atom is more mobile than that of the Fe(1) atom. Spectral studied demonstrates that the high-spin Fe^{III} ions are antiferromagnetically coupled to produce the diamagnetic ground state.[109] According to X-ray diffraction, EPR and Mössbauer spectroscopy, reduced sMMO (see Fig. 2 *b*) contains two high-spin ($S = 2$) ferromagnetically coupled Fe^{II} atoms in different ligand environments. Upon the reduction, the distance between the iron atoms increases to 3.3 Å[91, 96] owing to the loss of hydroxyl bridges and the replacement of one of them by an oxygen atom of the carboxylate group bonded to the Fe(2) atom. As a result, two coordination sites of the Fe(2) atom are vacated and become capable of binding O_2.[97] This side of the binuclear complex borders with the hydrophobic substrate-binding pocket and is the place where the entire catalytic process occurs. Binding of protein B leads to a change in some spectral characteristics of the reduced Fe_2 cluster, which points to possible changes in the coordination environment of one iron atom, presumably Fe(2).[102]

The hydroxylase component of sMMO also contains a hydrogen bond network extended from the binuclear moiety to the protein surface, which serves to transfer protons and, perhaps, electrons to the reaction zone. DFT calculations of the electronic and geometric structures of ferri- and ferro-sMMOs have shown that the protein environment has a noticeable effect on the active site energetics.[107, 110]

The dithionite-reduced hydroxylase component ($\mathbf{H}_{red}$) can accomplish stoichiometric oxidation of methane by dioxygen (one cycle) in the absence of reductase. The addition of methane in this case has only a moderate effect on the oxygen uptake rate.[92]

The catalytic cycle of sMMO (Scheme 2) [97] shares some similarities with the catalytic cycle of cytochrome P450, although there are important differences. Optical spectroscopy (stopped-flow technique)[111, 112] allowed the authors to reveal and characterize key intermediates, **P** (or $\mathbf{H}_{peroxo}$) and **Q**, formed in the reaction of ferro-sMMO with O_2 in a native system. These compounds accumulate in noticeable concentrations before they react, but their exact structure is

Scheme 2



$\mathbf{H}_{ox}$ is the oxidized form of the hydroxylase active site, S is a substrate, and S_{ox} is the oxidized substrate form.
The rate constants of the corresponding stages are given.

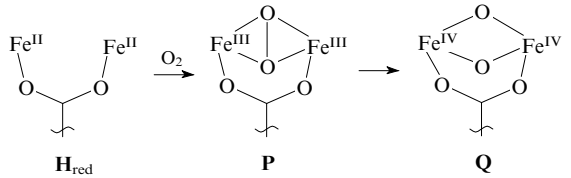
still the subject of much debate. The first observed intermediate is peroxodiiron(III) **P**. There is indirect evidence of formation of its precursor, intermediate **P***, which can be a peroxo or superoxo complex.[97, 113] The presence of only one quadrupole doublet in the Mössbauer spectrum of intermediate **P** points to a symmetric arrangement of the peroxide group between the iron atoms. Compound **P** spontaneously converts to intermediate **Q**. The formation rate of **Q** is independent of methane addition, while its consumption rate is in direct proportion to the methane concentration. This fact enabled the conclusion that intermediate **Q** is a species reacting with methane. The consumption of compound **Q** in the reaction with methane is monitored by observing the decrease in its characteristic absorption spectrum.

Protein B plays a decisive role in key steps of the catalytic process:[101–103] in the presence of protein B, the O_2 binding rate increases almost 1000-fold; the rate of formation of intermediate **Q** increases 40-fold; the product yield increases from 40% to 80% and, when reductase is also present, to 100%. In the absence of the substrate, intermediate **Q** slowly converts to ferri-sMMO, taking two electrons and two protons, through formation of intermediate **Q***; the structure of the latter is still unknown, and it is unable to oxidize methane.[97]

Efficient and specific transformation of methane to methanol requires the creation of a potent oxidant and, simultaneously, the control of access of potentially more reactive substrates to this oxidant. The potent oxidant of sMMO — intermediate **Q** — is reliably protected by a closed protein structure. Quick access of methane and O_2 to intermediate **Q** becomes possible only when protein B forms a complex with oxygenase, generating a physical channel specific to the size of methane and O_2.[104] In the absence of the substrate, intermediate **Q** can accumulate in concentration sufficient for spectral studies. The Mössbauer spectrum of frozen solutions of compound **Q** shows that the iron atoms in it are in the high-spin state ($S = 2$) and are antiferromagnetically coupled (the coupling constant is $J < -30$ cm), forming a symmetric diamagnetic cluster $Fe^{IV}-O-Fe^{IV}$.[114]

The bridge mechanism of O_2 activation and methane oxidation, suggested more than ten years ago[115–117] and named in such a way to distinguish it from the terminal mechanism of O_2 activation in the mononuclear active site of cytochrome P450, took into account the role of the binuclear structure of the active site in MMO. According to this mechanism, intermediate **Q** was assigned as the $Fe_2^{IV}(\mu\text{-}O)_2(\mu\text{-}COO)$ cluster, and intermediate **P** was suggested to have a μ-1,2-peroxide structure or a bridged peroxide structure similar to compound **Q** in which each oxygen atom of the O_2 molecule is bonded to two iron atoms (Scheme 3).

Scheme 3



The mechanism implies that dioxygen activation occurs *via* homolytic O–O bond cleavage in the peroxide intermediate and does not involve a proton, while methane is activated by the attack of the bridging oxygen atom (as distinct from the terminal oxygen atom of the ferryl intermediate), presumably with the participation of the μ-oxo bridge. In subsequent years, this mechanism has been experimentally[118, 119] and theoretically[120, 121] proved and has been somewhat modified. In particular, EXAFS evidence has revealed that intermediate **Q** has one short and one long Fe–O bond and an extraordinary short distance between the iron atoms.[118] The length of 1.8 Å for the short Fe–O bond is longer than those of the terminal Fe=O bonds in high-valence iron porphyrin complexes (1.67 Å)[122] and in other ferryl complexes but is comparable with Fe–O distances in binuclear μ-oxo complexes containing the Fe–O–Fe moiety. Model complexes with the $Fe_2(\mu\text{-}O)_2$ core have been characterized,[123] and this structure has been supported by theoretical calculations.[121]

Currently, there are considered two mechanisms of conversion of intermediate **P** to intermediate **Q**, involving either homolytic[115, 121] or heterolytic[109, 124] O–O bond cleavage. The first mechanism occurs without protons and is akin to the mechanism of dioxygen activation by the Cu_2 cluster of tyrosinase (see below). This mechanism implies that electrophilic iron ions rather than protons function as O^{2-} acceptors. The second mechanism requires double protonation of one of the O atoms of the peroxide bridge resulting in the transformation of μ-1,2-peroxide to μ-1,1-peroxide and is akin to the mechanism of O_2 activation by cytochrome P450. The homolytic mechanism is supported mainly by theoretical calculations[120, 121] and by the synthesis of complexes containing the $Fe_2(\mu\text{-}O)_2$ core with characteristics similar to those of intermediate **Q**.[125] The heterolytic mechanism is supported, first of all, by kinetic studies of sMMO isolated from *Mt* in the absence of the substrate.[124] On the basis of the pH dependence of reaction rates and the consumption of protons, it has been suggested that two protons are required for O_2 binding: one proton for formation of intermediate **P** and the other, for its conversion to **Q**.[124] The role of protons in O_2 activation has long remained debatable since there were discrepancies in the results for sMMOs isolated from *Mt*[124] and *Mc*,[97, 119] presumably associated with different experimental procedures.[97] In recent years, these contradictions have been removed by additional studies.[126, 127] The mechanism turns out to be more sophisticated[128–130] than it was previously believed.[124] It was shown that, in the case of sMMO isolated from *Mc*, proton transfer is the rate-limiting stage in the transformations of intermediates **P*** → **P** and **P** → **Q**.[126] Theoretical calculations and studies of chemical models suggested that the first proton is transferred to the oxygen atom of the carboxylate bridge in reduced sMMO rather than to the peroxide.[128, 129] However, the exact structure of the intermediates of the MMO catalytic cycle remains unknown,[97] and the question of what mechanism is responsible for it still awaits its answer.

2. Iron complexes as structural and functional sMMO models

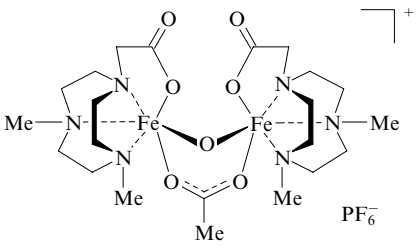
Some aspects of chemical modelling of sMMO have been addressed in several reviews.[131–140] In most works, binuclear iron complex–H_2O_2–MeCN–cyclohexane systems have been used, and relatively few works have focused on methane oxidation *per se*. Some binuclear iron complexes have been studied as structural and spectral models of the

active site of sMMO, and to a lesser extent, as functional models.

Methane was oxidized by dioxygen with low efficiency in the presence of complexes self-assembled on the silica surface modified with imidazole groups.[141] The comprehension of the necessity to have labile coordination sites in the metal coordination sphere led to the synthesis of the $[Fe_2O(2,2'\text{-bipy})_2(OBz)_2(H_2O)_2](ClO_4)_2$ complex (bipy is bipyridine).[142] In the presence of H_2O_2, this complex catalyzes the oxidation of methane and other alkanes at room temperature.[143] The increase in the alcohol yield with adding $HClO_4$ and the noticeable isotope effect ($k_H/k_D = 3.1$) in the case of cyclohexane hydroxylation have been interpreted as evidence of the heterolytic decay of coordinated peroxide resulting in an active ferryl intermediate that attacks an alkane.

To verify this assumption, the simplest binuclear complexes with labile coordination sites of general formula $[Fe_2OL_4(H_2O)_2](ClO_4)_4$ [L = 2,2′-bipy, 4,4′-dimethyl-2,2′-bipyridine, 4,4′-di(chloromethyl)-2,2′-bipyridine, 1,10-phenanthroline, 5-nitro-1,10-phenanthroline] have been synthesized and their catalytic activity in oxidation of methane and other alkanes has been studied.[144] The facts that (i) the catalytic activity depends on the nature of the substituent in the ligand in oxidation of methane and cyclohexane, (ii) the oxidation of *cis*- or *trans*-dimethylcyclohexane occurs with retention of configuration, (iii) the cyclopropane ring remains largely intact upon the oxidation of *trans*-1-methyl-2-phenylcyclopropane, and (iv) alkene oxidation leads to formation of epoxides, are evidence of the contribution of the ferryl (two-electron) mechanism of oxidation.[145, 146]

Binuclear μ-oxodiiron complex **8** with 1-carboxymethyl-4,7-dimethyl-1,4,7-triazacyclononane as a ligand

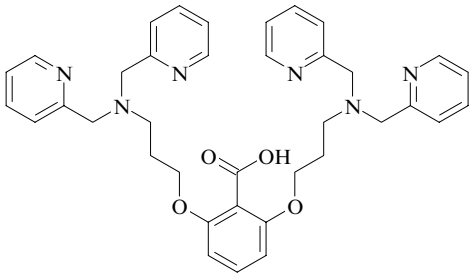


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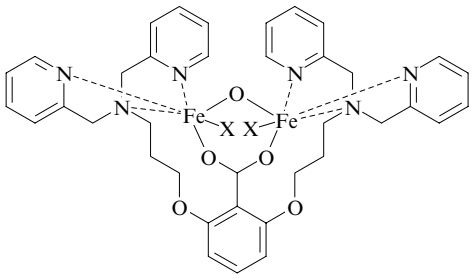
catalyzes the oxidation of methane with hydrogen peroxide in water at 50–80 °C to give methanol and methyl hydroperoxide with a total turnover number up to 25 catalytic cycles in 4 h.[147] The observed selectivity and specificity of the oxidation of other alkanes with hydrogen peroxide in acetonitrile catalyzed by complex **8** allows the authors [147] to suggest the participation of metal–oxygen intermediates in the reaction. As has been recently shown, formation of methyl hydroperoxide does not contradict such a mechanism.[148]

Binuclear μ-oxodiiron complexes are hydrolyzed with water,[149] which is ubiquitous in catalytic systems with hydrogen peroxide. This raises the question as to whether the active species is mono- or binuclear. To control the nuclearity of intermediates, polydentate dinucleating (coordinating two metal nuclei) framework ligand **9** and corresponding iron complex **10** were synthesized.[150–152]

An essential feature of the structure of this complex is the existence of labile coordination sites in arrangement suitable for the realization of the bridge mechanism. Complex **10** catalyzes the oxidation of methane to methanol with hydrogen peroxide at room or slightly elevated temperature (2–7 catalyst turnovers at 20–60 °C).



9

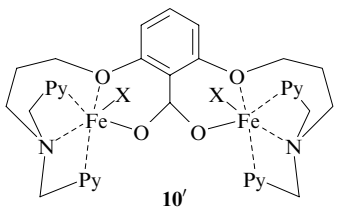


10

X is a labile ligand (H_2O or 1/2 carboxylate).

The experiments with cyclohexane and *cis*-1,2-dimethylcyclohexane showed the signs of the monooxygenase mechanism of alkane oxidation, in particular, the incorporation of the ^{18}O atom from labelled water in the product and the high stereoselectivity of the process.[153–155] According to electrospray ionization mass spectrometry (ESI-MS), the binuclear structure of the complex persists down to micromolar concentrations in a catalytic solution owing to the preorganized framework ligand. Therefore, it can be suggested that, first, a binuclear bridging peroxide forms at the labile coordination sites, which then converts to a binuclear ferryl intermediate. The latter is confirmed by the fact that the resulting alcohol contains the oxygen label from the labelled water introduced in the reaction. The low efficiently of oxygenation can be associated with the insufficient stability of the active complex in solution because of the flexibility of the framework ligand.

Inasmuch as the reduced form of sMMO is functionally active in nature, an iron(II) complex with the same ligand **9** was synthesized as a possible model of the reduced sMMO, and its reactions with O_2 and H_2O_2 in the presence and absence of an alkane has been studied. However, according to X-ray crystallography data, instead of the expected formation of the second bridge between the iron atoms



10′

X is OTf; Py is 2-pyridyl (coordination through the N atom).

involving the labile ligand, the ester oxygen atoms of the ligands are coordinated to the iron atoms so that the carboxylate group is twisted to adopt the unusual *anti*,*anti* configuration in rather rigid structure **10′**.

This leads to an increase in the Fe···Fe distance and the impossibility of formation of the bridged peroxide intermediate, which is a necessary condition of dioxygen activation. As a result, ferrous complex **10′**, unlike ferric complex **10**, mimics neither the structural nor the functional features of the active site of sMMO since it does not catalyze alkane oxidation reactions with hydrogen peroxide or O_2. It is likely that this fact is also responsible for the low activity of $Fe^{III}-H_2O_2$ models with ligand **9** since the initially active complexes can convert to inactive complexes because of the insufficient rigidity of the framework ligand. A common disadvantage of early works dealing with modelling sMMO is the lack of reliable proofs (for example, by means of isotope methods) of formation of methanol from methane with the participation of ferryl intermediates rather than $HO^{\bullet}$ radicals since such processes are, in principle, possible.[156]

Other approaches to modelling the active site of sMMO are also known in the literature;[135, 157, 158] however, none of them has resulted in the efficient biomimetic oxidation of methane. The nature of intermediate **Q** and its structure and reactivity, as well as the mechanism of its formation from the peroxide intermediate, are still inadequately understood. The cyclic structure of intermediate **Q** as a binuclear bis(μ-oxo)diiron complex (Scheme 3) is commonly accepted; however, it is not ruled out that the reactive species has an open structure [116, 159]

$$Fe^{IV}=O-\text{protein}-Fe^{IV}=O \text{ or } Fe^{III}-O-Fe^{V}=O.$$

In this context, studying mononuclear ferryl complexes and elucidating the nature of interaction between the iron atoms being in the same and different oxidation states in a binuclear complex have become of great importance.[139, 159]

The first mononuclear non-haem $Fe^{IV}=O$ complex has been obtained by the reaction of ozone with an iron cyclam (1,4,8,11-tetraazacyclotetradecane-1-acetate) complex at −80 °C and characterized in solution by Mössbauer spectroscopy.[160] Evidence for the participation of the ferryl intermediate in the non-haem environment in O atom transfer with insertion into the C−H bond has been obtained for a system with a tetradentate ligand — bis(2-pyridylmethyl)ethylenediamine (bpmen) — in the hydroxylation reaction of cyclohexane with hydrogen peroxide in the presence of $H_2{}^{18}O$ [161] (see also Ref. 145). The incorporation of the ^{18}O atom into the resulting alcohol is caused by the well-known exchange of the ferryl intermediate with labelled water, whereas its precursor, the hydroperoxide intermediate, is incapable of such an exchange.[161]

Binuclear oxo-bridged high-valence iron complexes $[Fe_2(\mu\text{-}O)_2L_2](ClO_4)_3$, where L is tris(2-pyridylmethyl)amine (tpa) and its alkyl derivatives have been synthesized.[162] These complexes mimic the putative bis(μ-oxo)-bridged structure of intermediate **Q** and model oxidative reactions of monooxigenases.[162] The $[Fe_2(\mu\text{-}O)_2(5\text{-}Et_3tpa)_2](ClO_4)_3$ [5-Et_3tpa is tris(5-rthyl-2-pyridylmethyl)amine] complex has been studied by X-ray crystallography, and the geometric parameters of the $Fe^{IV}(\mu\text{-}O)_2Fe^{III}$ core have been determined.[163] It has been shown that the $[Fe_2^{II}(\mu\text{-}OH)_2(6\text{-}Me_3tpa)_2](ClO_4)_2$ complex [6-Me_3tpa is tris(6-methyl-2-pyridylmethyl)amine] binds O_2 at −40 °C to form a bridged peroxide, which slowly converts at −3 °C to a complex with the $Fe^{IV}(\mu\text{-}O)_2Fe^{III}$ core, presumably through the formation of the $Fe^{IV}(\mu\text{-}O)_2Fe^{IV}$ intermediate.[164] Likewise, $Fe_2^{II}(\mu\text{-}O_2CAr)_4(4\text{-}Bu^tPy)_2$ (Ar = 2,6-Ph_2-4-MeC_6H_2, 4-Bu^tPy is 4-*tert*-butylpyridine) at −78 °C forms the $Fe^{IV}(\mu\text{-}O)_2Fe^{III}$ complex with O_2.[165] Complexes with the $Fe^{IV}(\mu\text{-}O)_2Fe^{III}$ core are able to oxidize only weak C−H bonds.[166] This result is not surprising. It might be expected that the postulated active oxidant sMMO with the $Fe^{IV}(\mu\text{-}O)_2Fe^{IV}$ core should be more active since it is capable of overall two-electron O atom transfer with the actual insertion into the C−H bond. This process is thermodynamically more favourable than the one-electron H atom abstraction process.[116] Indeed, the reaction of the $Fe^{IV}(\mu\text{-}O)_2Fe^{III}$ complex with ethylbenzene is 3 000 000 times as slow as the reaction of intermediate **Q** with methane: the second-order rate constants are, respectively, 5×10^6 and 16 litre $mmol^{-1}$ s^{-1}.[116]

An open ferryl form of the $Fe^{IV}(\mu\text{-}O)_2Fe^{IV}$ intermediate has been synthesized.[167] It turned out that the complex with the $Fe^{III}(\mu\text{-}O)_2Fe^{III}$ core is oxidized by the strong one-electron oxidant Ce^{IV} to give the terminal ferryl $Fe^{III}-O-Fe^{IV}=O$ complex, presumably through the stage of formation of the cyclic $Fe^{IV}(\mu\text{-}O)_2Fe^{III}$ intermediate. A similar isomerization has also been predicted by quantum chemical calculations for intermediate **Q**.[121] It was recently shown that the opening of the $Fe^{IV}(\mu\text{-}O)_2Fe^{III}$ ring leads to a complex with the $HO-Fe^{III}-O-Fe^{IV}=O$ core, which is one million times more reactive than its precursor in the reaction with C−H compounds.[157, 159] This increase in activity is, likely, contributed by three factors: formation of the terminal ferryl complex, the change in the spin state of the Fe^{IV} atom from $S = 1$ to $S = 2$ and, finally, concentration of the oxidative ability at the terminal oxygen atom of the oxo group as a result of conversion of the valence-delocalized complex to the valence-localized one:

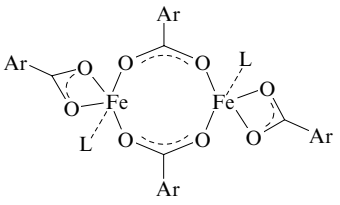
$$[Fe^{3.5}(\mu\text{-}O)_2Fe^{3.5}]^{3+} \longrightarrow [HO-Fe^{III}-O-Fe^{IV}=O]^{2+}.$$

Catalysis of hydroxylation of unactivated C−H bonds and epoxidation of double bonds by model complexes with nitrogen-containing donors is usually assigned to the participation of perferryl intermediates in the Fe^{III}/Fe^{V} catalytic cycle:[168, 169]

$$Fe^{III} + H_2O_2 \longrightarrow Fe^{III}OOH \longrightarrow Fe^{V}=O + RH \longrightarrow$$
$$\longrightarrow Fe^{III} + ROH$$

The formation of the hydroperoxide intermediate has been reliably detected by different methods at −40 °C in MeCN.[170] Since the $Fe^{III}OOH$ intermediate is unable to activate strong C−H bonds, is has been suggested that its heterolytic splitting leads to the oxoperferryl ($Fe^{V}=O$) intermediate which is actually an active oxidant. Recently,[171, 172] this intermediate was identified by EPR at −70 °C.

The synthesis of the Fe^{II} complexes of general formula $[Fe_2(O_2CAr)_4L_2]$ (**11**), containing bulky aryl groups, is an important breakthrough in modelling the structure of the binuclear site of sMMO.[173, 174]



11

Ar = 2,6-$Mes_3C_6H_3$ (Mes = 2,4,6-$Me_3C_6H_2$), 2,6-(4-$MeC_6H_4)_2$.C_6H_3; L = 4-Bu^{t}Py, Py, MeCN, THF.

The wealth of factual material on the synthesis and properties of these complexes has been covered in reviews.[135,139] The reaction of complex **11** (L = 4-Bu^{t}Py and Py) with O_2 at −78 °C in dichloromethane or toluene yields an equimolar mixture of $Fe^{II}Fe^{III}$ and $Fe^{III}Fe^{IV}$ complexes, presumably as a result of interaction of the forming analogue of intermediate **Q** with the initial complex:

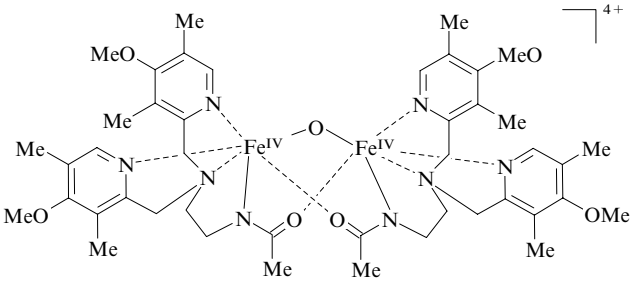
$$Fe^{II}Fe^{II} + O \longrightarrow Fe^{III}-O-O-Fe^{III} \longrightarrow Fe^{IV}(\mu\text{-}O)_2Fe^{IV},$$

$$Fe^{IV}(\mu\text{-}O)_2Fe^{IV} + Fe^{II}Fe^{II} \longrightarrow Fe^{II}(\mu\text{-}O)_2Fe^{III} + Fe^{III}(\mu\text{-}O)_2Fe^{IV}.$$

Complexes **11** successfully model the nearest coordination environment of the binuclear site of sMMO, containing two Fe^{II} ions, two carboxylate bridges and one terminal carboxylate group and one imidazole ring at each iron atom. However, they do not mimic finer features of the site structure (*syn*-configuration of nitrogen-containing donors, H_2O coordination) and many effects caused by the protein globule, such as substrate binding in a neighbouring hydrophobic 'pocket' and constraints caused by the polypeptide scaffold. Recently, framework Fe^{II} carboxylate complexes mimicking some of the effects have been synthesized.[139]

The first synthetic complex that partially mimics the probable $Fe^{IV}(\mu\text{-}O)_2Fe^{IV}$ structure of the active intermediate of sMMO was prepared by electrochemical oxidation of $Fe^{III}Fe^{IV}$ precursor[175] or by direct interaction of the Fe^{III} μ-oxo complex with hydrogen peroxide in the presence of perchloric acid.[176] In the latter case, in the absence of perchloric acid, a complex with the $[HO-Fe^{III}-O-Fe^{IV}=O]^{3+}$ core was isolated,[177] and its treatment with perchloric acid gave an intermediate **Q** analogue. If it is assumed that the peroxide intermediate should form first in the course of reaction, this is the first example of chemical modelling of transformation of intermediate **P** to intermediate **Q**. Experiments with ^{18}O have shown that a major part of the $Fe^{IV}(\mu\text{-}O)_2Fe^{IV}$ complex contains both oxygen atoms from hydrogen peroxide, which is evidence of the homolytic mechanism of peroxide bond cleavage (see above). However, there is a noticeable contribution of the $^{16}O^{18}O$ isotopomer, which is consistent with the heterolytic mechanism, as in the case of cytochrome P450. These experiments also point to a possible role of proton in the conversion of intermediate **P** to **Q**. Although the new complex formally models the core of intermediate **Q** (without the bridging carboxylate group), its activity turned out to be much lower. This confirms that the unprecedented reactivity of intermediate **Q** in the reaction with methane is caused by a multitude of fine structural factors that have yet to be learnt.

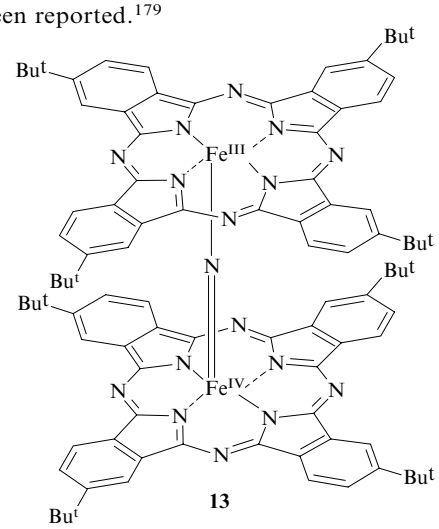
The recently synthesized complex **12** is most reactive among the known binuclear Fe^{IV} complexes



12

and is able to attack C−H bonds of strength up to 100 kcal mol^{-1}.[178] Complex **12** reacts with cyclohexane 100–1000 times faster than a mononuclear Fe^{IV} complex with an analogous ligand. Complex **12** has the (μ-oxo)-di(μ-carboxamido)Fe_2^{IV} core and has the highest redox potential among all known Fe^{IV} complexes; however, it functions as a one-electron oxidant with respect to C−H bonds. The oxidation rate of cyclohexane by complex **12** is one order of magnitude lower than the rate of methane hydroxylation with intermediate **Q**. It is not unlikely that the different spin states (see above) of the iron atoms or the lack of the second oxygen bridge is responsible for such a behaviour.

The efficient catalytic oxidation of methane by hydrogen peroxide in water to MeOH (traces), CH_2O and HCO_2H at 25–60 °C with the participation of the well-characterized binuclear N-bridged iron tetra(*tert*-butyl)phthalocyanine complex $[(PcBu^t_4)Fe^{III}-N=Fe^{IV}(PcBu^t_4)]$ (**13**) ($H_2PcBu^t_4$ is 2,9,16,23-tetra-*tert*-butyl-29*H*,31*H*-phthalocyanine) has been reported.[179]



13

The maximal total turnover number of the catalyst achieved in this process was 210 catalytic cycles, and the yield of the products as calculated for peroxide was 30%–50%. It is most significant that spectral and isotope studies directly point to the participation of the peroxide

$$[HOO-Fe^{III}(PcBu^t_4)-N=Fe^{IV}(PcBu^t_4)]^-$$

and ferryl

$$[O=Fe^{V}(PcBu^t_4)-N=Fe^{IV}(PcBu^t_4)] \longleftrightarrow$$

$$\longleftrightarrow [O=Fe^{IV}(PcBu^t_4)^{+\bullet}-N=Fe^{IV}(PcBu^t_4)]$$

intermediates in this reaction,[179–182] modelling the catalytic cycle of monooxygenases. However, theoretical calculations reveals that this system shares similarity with haem oxygenases of the cytochrome P450 type,[183] the $-N{=}Fe^{IV}$ moiety being treated simply as the *trans*-axial $O{=}Fe^{V}$ ligand of phthalocyanine, similar to OH or NH_2 groups. On the other hand, from the viewpoint of modelling sMMO, this system is nevertheless nonselective for methanol, which accounts for the smallest fraction of the oxygenation products.

Table 2 summarizes characteristics of the most interesting chemical analogues of oxygenases, including those discussed below. As is seen, metals other than iron can also be involved in immobilization of the O atom and its transfer with the insertion into the C–H bond. Systems Nos 1–3, 5 and 7 use active oxygen carriers and are similar to shunt systems in biological oxidation. On the other hand, systems Nos 4, 6 and 8 use O_2 and can be considered complete models of oxygenases. The catalyst in system No. 4 is complex **14** with the salicylidene ligand and that in system No. 5 is the iron-containing zeolite FeZSM-5. It is worth noting that systems Nos 5–7 do not contain organic ligands at the metal atom and are purely inorganic analogues of oxygenases. Most systems are characterized by high selectivity to methanol (90%–100%), but often at low methane conversion. It should be noted that the same selectivity can be attained in flow-type noncatalytic or heterogeneous catalytic systems at high temperature and short contact times.[189]

In practical terms, the most interesting system among those in Table 2 is system No. 7, which prevides high selectivity to methanol (88%) at a rather high current efficiency (61% at the anode potential +900 mV) in a flow regime at ambient pressure and 100 °C. The process is carried out in an electrochemical reactor of the fuel cell type, with the cathode and anode separated by a proton-conducting membrane. A mixture of methane and steam is fed to the anode, while air is fed to the cathode. Although the selectivity of the process is < 100%, there is no problem with separation since methanol is the only liquid product at ambient temperature. The by-product (CO_2) is formed at other sites located on the support (SnO_2). On the basis of available data,[187,189] it can be suggested that the active sites in this system are binuclear surface complexes $(V^{V}-O^{\bullet})_2$ formed at the anode upon the oxidation of vanadium aqua complexes and, presumably, similar to intermediate **Q**. The tin atoms are likely involved in the formation of active vanadium sites, acting as inorganic ligands of vanadium, just as do aluminium atoms in the α-sites on the FeZSM-5 zeolite (see Section III.3). It is interesting that, although V_2O_5 exhibited the highest activity, close results were obtained for Fe_2O_3 and Au. Methanol can be obtained with high selectivity with the use of O_2 and electrons from the cathode (Cu/Pd/Au) by the classical oxygenase reaction

$$CH_4 + O_2 + 2e + 2H^+ \longrightarrow CH_3OH + H_2O. \quad (10)$$

However, in this case, the current efficiency is much lower than in the anode process because of the nonproductive consumption of electrons for the reduction of dioxygen to water.[187] Thus, system No. 7 is a functional model of MMO. An efficient structural and functional iron-based chemical model of sMMO is yet to be found. System No. 4 with ruthenium, an iron analogue,[184] is intriguing; however, the cited work raises many questions and its results should be revisited.

3. α-Sites and α-oxygen on iron-containing zeolites

Of great interest is the highly selective (94%) stoichiometric oxidation of methane to methanol by nitrogen(I) oxide at room temperature with participation of so-called α-sites on the FeZSM-5 zeolite surface (Table 2, system No. 5).[185] α-Sites are surface iron complexes $(Fe^{II})_\alpha$ formed in high-temperature treatment of FeZSM-5 owing to the thermal reduction of Fe^{III} to Fe^{II} with O_2 release.[190,191] These complexes are stabilized by the zeolite matrix so that the reverse oxidation with dioxygen becomes thermodynamically unfavourable.[192] However, surface iron complexes are readily oxygenated with N_2O at 200–250 °C to form long-lived oxygen intermediates $(FeO)_\alpha$, or $\alpha\text{-}O_{Fe}$, referred to as α-oxygen. They are able to give the oxygen atom to saturated hydrocarbons and H_2, benzene or carbon oxide molecules at room temperatures, thus returning, partially or completely, to the initial state $(Fe^{II})_\alpha$. Surface $(FeO)_\alpha$ intermediates cannot be formed under the action of O_2. The α-O–Fe bond energy is 60 kcal mol^{-1}, *i.e.*, approximately twice as low as the O_2 dissociation energy. Formation of α-oxygen and its reactions are two-electron processes. They formally resemble formation of ferryl intermediates *via* oxygen atom transfer from XO donors to Fe^{II} sites of iron-containing oxygenases in shunt processes (see above), as well as interaction of these intermediates

Table 2. Selective catalytic oxygenation of methane with chemical analogues of oxygenases.

System, No.	Catalyst	O source	Medium	T/°C	Products	Selectivity to MeOH (%)	TON (TOF /h^{-1})	Ref.
1	$[Fe_2OL_2(OAc)](PF_6)$ (**8**) [a]	H_2O_2	D_2O	80	MeOH, MeOOH	60	24 (6)	147
2	$[Fe_2OL(OBz)](ClO_4)_2$ (**10**) [b]	H_2O_2	MeCN, H_2O	60	MeOH	100	7	153
3	$[(FePcBu^t_4)_2N]$ (**13**)/SiO_2	H_2O_2	H_2O, 0.075 M H_2SO_4	60	HCO_2H, CH_2O, MeOH	90 [c]	210 (10)	180
4	$[Ru_2O(salen)_2(OAc)_2]$ (**14**) [d]	O_2/ [e]	H_2O, Me_2CO	30	MeOH, CH_2O	90	54 (50)	184
5	FeZSM-5	N_2O	gas phase	20	MeOH, Me_2O	94	1	185
6	CuZSM-5	O_2/Cu^{I}	the same	125	MeOH	98	1	186
7	V_2O_5/SnO_2	H_2O/anode	H_2O (vapour)	100	MeOH, CO_2	88	1	187
8	Au_3-rutin [f]	O_2/NADH	H_2O	25	MeOH	100	30	188

[a] L is 1-carboxymethyl-4,7-dimethyl-1,4,7-triazacyclononane; [b] L is ligand **9**; [c] the selectivity to HCO_2H is reported; [d] salenH is *N*,*N*′-ethylenebis(salicylideneamine); [e] there should be a reducing agent, which was not indicated by the authors; [f] see Section V for the complex formula.

with alkanes. This fact, the kinetic characteristics of such reactions and, finally, the ability to selectively oxidize methane to methanol at room temperature suggest $(Fe^{II})_\alpha$ complexes on the FeZSM-5 zeolite surface as a possible model of the active site of MMO.[193] The large kinetic isotope effect observed in methane oxidation ($k_H/k_D = 5.5-1.9$ at temperature from -50 to 100 °C) is evidence that the rate-limiting stage is the C—H bond cleavage.[194]

Similarities and differences between $(FeO)_\alpha$ and active oxygen intermediates of MMOs have been discussed in a number of works (see, *e.g.*,[193–196]). However, there is still no consent on the geometric and electronic structures of $(Fe^{II})_\alpha$ and $(FeO)_\alpha$, as well as on the mechanism of methane oxygenation on the FeZSM-5 zeolite. The properties of α-oxygen and the iron atom state in $(Fe^{II})_\alpha$ and $(FeO)_\alpha$ have been studied experimentally[194–199] and theoretically[200–205] and surveyed in recent reviews.[206,207] Studying $(Fe^{II})_\alpha$ and $(FeO)_\alpha$ by spectral methods presents difficulties because of the extremely low concentration of α-sites (0.1 mass % – 1 mass %; however, the α-sites in these samples account for ~50% of the overall iron content) and the presence of different iron forms in an active FeZSM-5 sample.

A controversial issue is the nuclearity of α-sites. Binuclear[193,208,209] and(or) mononuclear[201,210] sites, as well as the presence of an aluminium atom as a possible ligand in the first coordination sphere,[195,209] have been suggested. In early studies,[132,193] the binuclear nature of α-sites has been proposed on the basis of the similarity of the Mössbauer parameters of hydrated $(Fe^{III})_\alpha$ and $(Fe^{II})_\alpha$ to the corresponding parameters of the oxidized and reduced sMMO forms. Mössbauer spectroscopy revealed two types of long-lived $(FeO)_\alpha$ intermediates with the isomer shift corresponding to the Fe^{III} state of the iron atom.[211] Following the logic of comparison of α-sites with MMO and taking into account a definite similarity of the Mössbauer parameters of their active oxidants, one could assume that the two $(FeO)_\alpha$ intermediates correspond to intermediates **P** and **Q** for sMMO. One of the $(FeO)_\alpha$ intermediates, according to the measured isomer shift $\delta = 0.58$ mm s^{-1}, could be the peroxide intermediate. However, according to the isomer shift for the other intermediate $\delta = 0.38$ mm s^{-1}, the inorganic analogue of intermediate **Q** should have the $Fe^{III}-O^{\bullet}$ structure isoelectronic with the $Fe^{IV}=O$ moiety. Effectively, it is the $Fe^{IV}=O$ complex, just as $Por^{+\bullet}Fe^{IV}=O$ [an active intermediate of cytochrome P450 (Por is porphyrin)] is effectively the $PorFe^{V}=O$ complex. Therefore, it is acceptable to call the former 'ferryl intermediate'.

The activity of ferryl complexes is often believed to be associated with the admixture of $Fe^{III}-O^{\bullet}$ oxyl excited states in their electronic structure.[212,213] Formation of these species is recognized an important step on the path to the transition state of the C—H bond oxygenation reaction.[214] The electronic structure of the $Fe^{III}-O^{\bullet}$ type for the $(FeO)_\alpha$ analogue of intermediate **Q** is also supported by other methods.[215,216] Factors that have an effect on the interconversions of $Fe^{IV}=O$ and $Fe^{III}-O^{\bullet}$ have been examined.[202]

Mössbauer studies have shown than the activated FeZSM-5 zeolite contains two types of $(Fe^{II})_\alpha$ species that react with N_2O to give two types of $(FeO)_\alpha$ intermediates.[217,218] Both intermediates disappear in the reaction with methane, and it is possible that their difference is caused by different structures of α-sites.[218] However, the kinetic study results indicate that both $(FeO)_\alpha$ types have the same reactivity or rapidly interconvert. The peroxide intermediate of α-sites was also characterized by UV-Vis and Raman spectroscopy.[219] When treated with benzene, this intermediate disappears, and the spectrum shows the signals of phenol coordinated to the iron atom. The band at 867 cm^{-1} was assigned[219] to ν(O—O) vibrations in the putative binuclear peroxide, which undoubtedly corresponds to one of the $(FeO)_\alpha$ intermediate. However, additional isotope measurements are necessary for the correct assignment of this band.

Mössbauer spectroscopy is the most efficient method for determining the iron state in FeZSM-5. To determine the actual structure of α-sites, it would be expedient to compare the Mössbauer parameters calculated by the DFT method for possible structures with the experimental values. In addition to further comprehensive study of the structure of α-sites and the nature of the active intermediates involved in methane oxidation on FeZSM-5, serious effort is needed to turn this reaction into a catalytic processes similar to the efficient selective oxidation of benzene to phenol on FeZSM-5.[220] The results of the authors[218,221] show that this is in principle possible.

IV. Copper-based catalysts

1. Membrane-bound methane monooxygenase

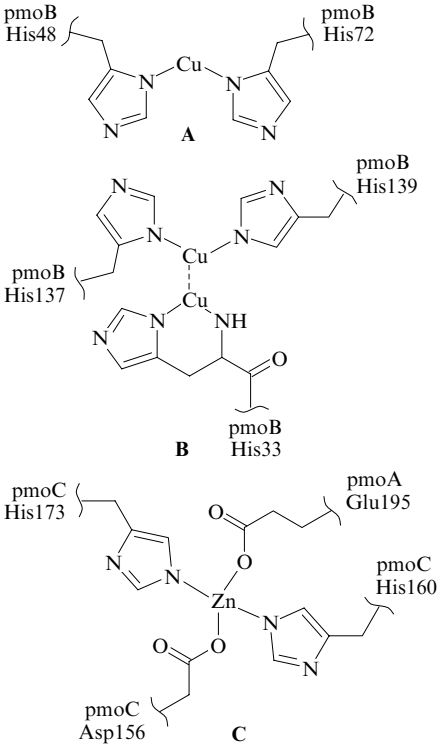
Whereas many features of the sMMO structure and function were discovered in the 20th century, an understanding of the structure and mechanism of function of membrane-bound MMO (pMMO) has begun only recently to emerge.[222] As noted above, cytoplasmic iron-containing sMMO is produced only by a few methanotroph species and only under low-copper conditions, whereas pMMO is produced by all methanotrophs and is an integral membrane-bound enzyme with copper biocomplex(es) as the active site. As distinct from sMMO, pMMO exhibits high substrate specificity and regio- and stereoselectivity. Both the hydroxylation and the epoxidation mediated by pMMO occur with retention of configuration at the oxidized site.[223]

The history of studying pMMO is full of contradictions and errors.[224,225] Three major hypotheses of the nature of the active site of pMMO have been considered in the literature: (i) it contains at least one but likely several trinuclear copper clusters (Cu_3) functioning as both the catalyst of methane hydroxylation and the electron-transfer agent;[223] (ii) the catalytic site, as in sMMO, is a binuclear iron cluster;[226,227] (iii) the catalytic site is a binuclear copper cluster.[228–230] Recent structural studies[222] confirm the last point of view. Most studies of pMMO have been performed on enzymes isolated from two bacteria strains: *Methylococcus capsulatus Bath* and *Methylosinus trichosporium OB3b*.

According to X-ray crystallography data,[228] the transmembrane protein pMMO from *Mc* consists of three subunits: pmoB, or α (molecular weight 47 kDa); pmoA, or β (24 kDa); pmoC, or γ (22 kDa). They form a trimer complex $(\alpha\beta\gamma)_3$ (see also Ref. 231). This complex can bind the methanobactin molecule, containing 6–8 copper ions and supplying copper to the active site of pMMO, which could be a reason for the emergence of the first hypothesis[223] (see above). The soluble regions of the enzyme originate from pmoB. There is a multitude of interconnections between

promoters and their constituent subunits, involving residues of each promoter in the soluble region and two helices from each pmoA. An important feature of the trimer is a funnel-shaped cavity at its centre, which is ~11 Å in diameter in the soluble region and is lined with charged residues. Inside the membrane, the cavity is lined with hydrophobic residues and gradually increases in diameter to 22 Å at the end opposite to the soluble region. The functionality of this cavity and the role of the trimeric structure remain unknown since the groups of metal centres of three promoters are rather distant from each other.

Inside each αβγ promoter, there are three discrete metal sites: mononuclear (**A**) and binuclear (**B**) copper biocomplexes in the soluble region of pmoB, as well as 'zinc centre' **C** inside the membrane in pmoC.



The mononuclear Cu site, located ~25 Å above the membrane surface, is coordinated by two almost linearly arranged histidine residues and, presumably, one or two water molecules. At a distance of ~21 Å from it and 11 Å above the membrane, there is the binuclear site coordinated by three histidine residues and an amino group, while the other ligands can be water molecules or fragments. According to X-ray crystallography and EXAFS evidence, the distance between the copper atoms in it is ~2.6 Å. A hydrophobic cavity capable of binding methane is adjacent to the binuclear site.[228] The mononuclear and binuclear sites are located in the β subunit at a distance sufficient for direct electron transfer. At a distance of ~19 Å from the binuclear site, a nonphysiological 'zinc site' is located within the lipid bilayer, its name reflecting the fact that it incorporates a zinc ion from the crystallization buffer solution. This site is formed by two histidine residues and two carboxylate groups capable of coordinating one metal atom. Although no iron was found in the crystal structure, it is present in dissolved pMMO samples, presumably being substituted by zinc upon crystallization.

EXAFS and XANES data point to the presence of Cu^{I} and Cu^{II} in pMMO isolated from *Mc* cells, as suggested earlier,[232] and to the capability of Cu sites to undergo redox transformations when pMMO is treated with hydrogen peroxide or dithionite.[233] The Cu–Cu distances and the average Cu–heteroatom (O or N) distance increase upon reduction, whereas the treatment with hydrogen peroxide does not change the Cu–Cu distance, which demonstrates that the oxidation with peroxide does not change this site. EXAFS and crystallographic data on pMMO from *Mt* showed that this enzyme also contains a binuclear copper site like pMMO isolated from *Mc*.[234] However, the mononuclear site identified in the latter is absent in pMMO from *Mt*, and the 'zinc site' contains a copper ion rather than a zinc ion. The EPR spectrum shows a signal corresponding to the Cu^{II} atom in the tetragonal environment of imidazole ligands. This signal can arise either from the copper atom of the 'zinc site', or from the $Cu^{I}Cu^{II}$ site, or from both these sites. Structural and spectral studies[228,233–235] have produced no evidence of the presence of tricopper clusters, as previously suggested for the pMMO active site on the basis of EPR spectra.[223] The amino acid donors at the 'zinc site' are typical of the coordination environment of the iron atom in sMMO. In this context, it has been suggested that the protein purification and crystallization procedures lead to removal of the iron ion from such a site and its exchange for a zinc ion from the buffer.

The recent structural study[222] has significantly advanced the understanding of the nature of the active site in pMMO. It has been convincingly shown that the pMMO activity is dependent on copper, not iron, and that the Cu active site is located in the soluble domain of the pmoB subunit rather than within the membrane and, finally, that this is a binuclear rather than mononuclear site. This excellent work deserves more attention. The authors used recombinant DNA to express in *Escherichia coli* the modified pmoB protein, thus creating a simplified soluble analogue of pMMO, spmoB. Like pMMO, this model protein links three copper ions and is able to oxidize methane. Crystallographic and spectral (EXAFS) studies of this metalloprotein revealed a short Cu–Cu contact, which is evidence of the existence of the binuclear site. Mutations of the amino acid residues in the coordination environment of the mononuclear and binuclear sites confirmed the catalytic activity of the binuclear site. A natural question arises as to if spmoB is able to oxidize methane, why is pMMO a membrane protein? It is quite likely that the hydrophobic substrate is delivered through the lipid bilayer and, owing to the increased solubility of methane in the membrane,[236] this can ensure its higher local concentration.[222] Most likely, methanol leaves the enzyme through the soluble domain.

Although recent studies have considerably elucidated the structure of the active site of pMMO, the mechanism of methane oxidation by this monooxygenase is unknown. Candidates for the role of an active oxidant can be the mixed-valence $Cu^{II}Cu^{III}$ oxo complex or simply the $Cu^{II}Cu^{II}$ oxo site.[237] However, the former has not been identified or isolated among the family of Cu_2O_2 models, and the latter, even if obtained, has been inadequately studied.[237] According to theoretical calculations,[238,239] the mixed-valence bis(μ-oxo) $Cu^{II}Cu^{III}$ complex *per se* or incorporated in a trinuclear site is a stronger oxidant than the $(\mu\text{-}O)_2Cu_2^{III}$ complex or the corresponding peroxo complex $Cu_2^{II}(O_2)^{2-}$ and, unlike these complexes, it is able to oxidize

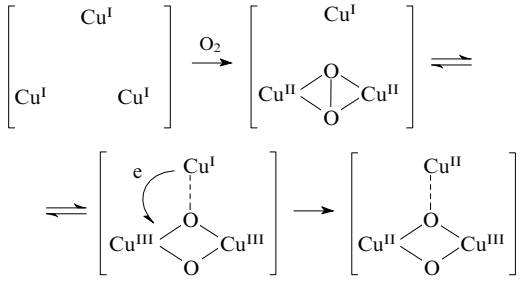
methane. It is suggested that methane oxidation occurs *via* the concerted mechanism involving direct insertion of a singlet oxygen atom (oxene) into the C–H bond.[239] The complete retention of the configuration at the oxidized carbon atom and excellent agreement between the observed and calculated KIEs ($k_H/k_D = 5$ at 300 K) are consistent with this mechanism.[239]

Copper-containing oxidases and oxygenases constitute a large class of enzymes employing different mechanisms for O_2 activation and oxidation of inorganic substrates.[240] In the context of studying O_2 activation with the binuclear active site of pMMO, the well-known binuclear copper-containing oxygenases, tyrosinase and catechol oxidase capable of catalyzing the oxidation of C–H bonds, are of definite interest. Tyrosinase and catechol oxidase in the reduced Cu^ICu^I state bind O_2 to form μ-η^2:η^2-peroxo complex,[241,242] which was structurally characterized for the first time for the copper-containing O_2 carrier, hemocyanin.[243] The O–O bond vibration frequency in such a complex (~750 cm^{-1}), measured by IR spectroscopy, is considerably lower than for most metal peroxide complexes (850–900 cm^{-1}), which implies significant O_2 activation upon its coordination to two Cu^{II} ions.

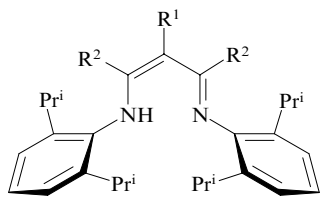
2. Copper complexes as structural and functional models of pMMO and other binuclear copper-containing oxygenases

Several interesting reviews are available covering the reactions of copper–oxygen complexes at C–H bond and the copper complex catalysis of oxidation of C–H compounds in the presence of O_2 or O atom donors.[244–249] Numerous copper(II) μ-η^2:η^2-peroxo complexes have been described some of which can reversibly convert to bis(μ-oxo)Cu_2^{III} complexes (Scheme 4) structurally similar to intermediate **Q** for sMMO.

Scheme 4



The Cu···Cu distance in the bis(μ-oxo)Cu_2^{III} moiety (~2.8 Å) is considerably shorter than in μ-η^2:η^2-peroxo-Cu_2^{II} (~3.6 Å) and is close to that in the binuclear copper site of pMMO (~2.6 Å). However, the $(\mu\text{-O})_2Cu_2^{III}$ structure was never observed in biological systems. The literature has mainly focused on cases of intramolecular oxidation mediated by such oxygen-containing complexes and almost exclusively for C–H bonds, while available examples of intermolecular reactions are extremely rare[250] and are completely lacking for methane.



14

R^1 = H, Me, CN, NO_2; R^2 = H, Me.

Hydroxylation of alkanes (including cyclohexane and adamantane) with hydrogen peroxide catalyzed by the copper(II) β-diketiminate complex LCuOAc, where L is ligand **14**, has been described.[251]

According to spectral data, the active intermediate is the bis(μ-oxo)Cu_2^{III} complex. The catalytic activity depends on electronic and steric effects of the substituents in the ligand. The oxidation of cyclohexane leads to cyclohexanol and cyclohexanone (in the ratio 3.7 : 1) with the total turnover frequency of 26 catalytic cycles per hour. The observed KIE ($k_H/k_D = 2.4$), high regioselectivity of the attack at the tertiary and secondary bonds of adamantane (5 : 1) and marked predominance of alcohol in the products are consistent with the mechanism of H atom abstraction by the oxo group of the active intermediate. To explain the second order in the bis(μ-oxo)Cu_2^{III} complex of the C–H bond oxidation reaction, intermediate formation of a tetranuclear copper complex or intermolecular disproportionation of binuclear complexes is suggested:[252]

$$2\,Cu^{III}Cu^{III} \longrightarrow Cu^{IV}Cu^{III} + Cu^{III}Cu^{II}.$$

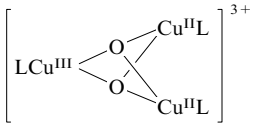
The formation in this way of a more active species seems to be quite probable since, as discussed in Section III.2, similar intramolecular disproportionation for intermediate **Q** ($Fe^{IV}Fe^{IV} \rightarrow Fe^{V}Fe^{III}$) should give a more active species capable of abstracting an H atom from alkane.

The binuclear copper(I) complex with a framework ligand formed by binding of two β-diketiminate moieties exhibited, in addition to the excellent stability, the high reactivity to O_2 and catalytic activity in oxidative binding of phenols and O atom transfer to phosphines.[253] The reaction of this complex with O_2 or PhIO at −80 °C yields a green intermediate that was spectroscopically identified as a $(\mu\text{-oxo})Cu_2^{II}O$ complex.

For the intramolecular oxidative N-dealkylation in bis(μ-oxo)Cu_2^{III} complexes, the site of attack of the ligand alkyl group is determined by the proximity and appropriate orientation of the attacked C–H bond to the lowest unoccupied molecular orbital (LUMO) σ* localized on the oxygen atom in the plane of the $(\mu\text{-O})_2Cu_2^{III}$ core.[254] Some observations (the large KIE value, sensitivity to the C–H bond dissociation energy at the same access to the attacked C–H bonds, kinetic parameters of the process) confirm the mechanism of H atom abstraction at the rate-limiting stage.[246] If a peroxo complex is introduced into the reaction, its conversion to bis(μ-oxo)-Cu_2^{III} complex usually becomes the rate-limiting stage.[255,256] Rare examples of oxidation of unactivated C–H bonds, such as in the β-CH_2 group of *N*-propylamine or in the methyl group of isopropylamine, in intramolecular reactions of oxidative N-dealkylation point to the possible reduction of the Cu_2O_2 core to the mixed-valence bis(μ-oxo)$Cu^{II}Cu^{III}$ complex, since these reactions occur only in the presence of a reducing agent.[257,258]

The above experimental results are supported by quantum chemical calculations,[238,239] emphasizing the oxidation power of mixed-valence binuclear Cu sites. Theoretical studies also show that a mononuclear analogue of ferryl — cupryl (Cu^{III}-oxo or Cu^{II}-oxyl) — can be sufficiently reactive to oxidize methane.[259,260] Indirect experimental data allow one to assume, in some cases, the participation of such species in oxidation of unactivated C–H bond in the

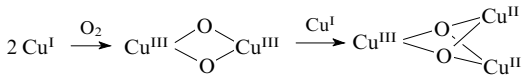
presence of copper complexes; however, no direct evidence is available.[261] The first crystallographically characterized tricopper complex $[Cu_3O_2L_3]^{3+}$ (**15**) [L is (1*R*,2*R*)-bis(dimethylamino)cyclohexane] with the $(\mu_3\text{-}O)_2Cu^{II}Cu^{II}Cu^{III}$ core,



15

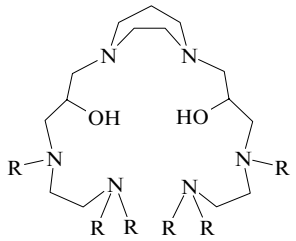
was synthesized *via* four-electron O_2 reduction with three equivalents of the Cu^I complex $[LCu^I(MeCN)]^+$.[262]

Analogously, the $Cu^{II}Cu^{II}Cu^{III}$ bis(μ_3-oxo) complex with dimethyl[2-(2-pyridyl)ethyl]amine has been synthesized.[255] This reaction occurs *via* the intermediate formation of the bis(μ-oxo)Cu_2^{III} complex:



The mixed-valence complex can abstract an H atom from phenols, but its activity in reactions with C–H compounds turns out to be low.

Based on the assumption of the trinuclear structure of the active site in pMMO and theoretical calculations of the methane hydroxylation reaction at a trinuclear site,[239] polydentate framework trinucleating ligands **16** were designed.



16

R = Me, Et.

With these ligands, unstable Cu_3^I complexes have been synthesized, which react with O_2 to form active $Cu^{II}Cu^{II}$-$Cu^{III}O_2$ intermediates as assumed on the basis of ESI-MS data (Scheme 4). These complexes turned out to be capable of inserting an O atom from O_2 into weak C–C bonds and, in the absence of a substrate, hydroxylated a very strong C–H bond in the methyl group of acetonitrile used as a solvent.[263] The mechanism of oxene insertion into the C–H bond was suggested on the basis of DFT calculations.[239] One oxygen atom is transferred to the substrate while the other one forms an oxo bridge with two copper atoms in the initial complex. This mechanism is similar to the bridge mechanism suggested for sMMO (see Section III.1). The resultant complex was isolated and characterized by spectral and crystallographic data.

The tricopper $[Cu_3(H_2tea)_2(4\text{-}HOC_6H_4CO_2)_2(H_2O)]$ complex (**17**) with the tetradentate triethanolamine ligand (H_2tea) (Fig. 3) catalyzes the oxidation of methane (TON = 47), ethane and cyclohexane with hydrogen peroxide in acetonitrile at 40 °C, but the mechanism of these transformations is unclear.[264] The unprecedentedly high catalyst turnover frequency (TOF = 600 h^{-1}) in cyclohexane oxidation was achieved in an analogous reaction in the presence of a tetracopper complex.[265] However, in the latter case, the major product was the corresponding alkyl hydroperoxide, and the putative reaction mechanism involved the attack of the alkane by the hydroxyl radical generated in the reaction of H_2O_2 with a copper(I) complex. Thus, the problem of creating a functional pMMO model based on copper complexes capable of hydroxylating methane still remains unsolved.

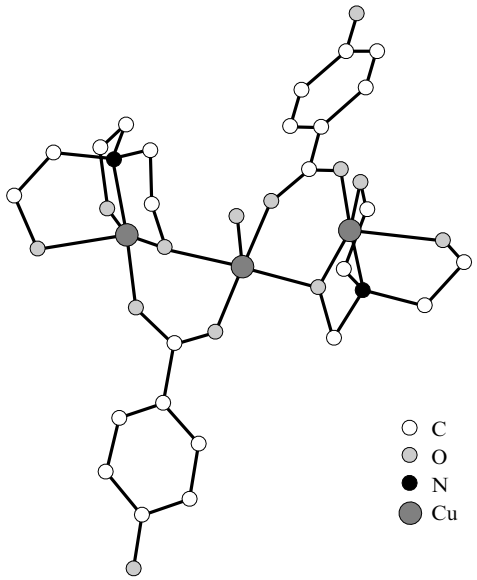


Figure 3. Structure of complex **17** (protons are omitted for clarity).[264]

3. Methane oxidation with dioxygen on copper-containing zeolites

α-Sites analogous to those on FeZSM-5 zeolites have been found on CuZSM-5 zeolites (as well as on CoZSM-5[266]), which is, presumably, first of all caused by the structure of zeolites of this type. The α-sites $(Cu^I)_\alpha$ are generated in the course of the high-temperature treatment of a metal-containing zeolite. They bind the O atom from N_2O to produce α-oxygen ($\alpha\text{-}O_{Cu}$) that is capable of selective oxidation of methane to methanol under mild conditions.[267,268] As in the case of the FeZSM-5 zeolite and the sMMO enzyme, the α-sites on CuZSM-5 and $\alpha\text{-}O_{Cu}$ can be treated as a model (at least, functional, but perhaps structural as well) of, respectively, the active site and active oxidant of pMMO.

Recently, interest in studying $\alpha\text{-}O_{Cu}$ has increased since, first, it is generated not only from N_2O but also from O_2 decomposition, and, second, it gives promise that the nature of the active oxidant in pMMO, which has resisted interpretation for 20 years, will be elucidated. It is important that, as distinct from $\alpha\text{-}O_{Fe}$ whose nature is still debatable, the structure of α-O on CuZSM-5 has recently been definitely proved.[269] Although similar Cu-containing zeolites catalyze the selective (98%) oxidation of methane and other lower alkanes to alcohols by dioxygen at 125 °C (see Table 2),[186,267] their activity is, presumably, lower than the activity of $\alpha\text{-}O_{Fe}$ oxidizing methane even at subzero temperatures.

Previously, on the basis of spectroscopic studies, it has been suggested that the active oxidant in CuZSM-5 has the

bis(μ-oxo)dicopper core.[186, 270, 271] The catalytic effect of this site correlates with an absorption feature at 22 700 cm^{-1}; according to EXAFS results, the Cu—Cu distance is 2.87 Å. The α-O_{Cu} sites account for ~5% of the total copper content in CuZSM-5. Different researchers have considered different structures (see, *e.g.*, Ref. 267), and theoretical calculations have predicted that both copper μ-η^2:η^2-peroxo and bis(μ-oxo) complexes are possible.[272] Because of the small fraction of α-O_{Cu} in the zeolite, its absorption band at 22 700 cm^{-1} was used for observing vibrations of this chromophore in a resonance Raman spectrum.[269] Absorption spectroscopy and resonance Raman spectroscopy in combination with DFT calculations and normal coordinate analysis made it possible to determine the geometric and electronic structures of the active oxidant in CuZSM-5 and the character of its activation for H atom abstraction from methane.[269]

On the basis of these data, the α-O_{Cu} site was uniquely assigned as a bent $[Cu-O-Cu]^{2+}$ core (delineated by the frame in Fig. 4), which was never previously observed and suggested as a catalytically active species. According to calculations, the Cu—O—Cu angle is 138–139°. It is likely that such a structure is dictated by the ZSM-5 crystal lattice, which determines the coordination environment of the bonded copper atoms and their spatial orientation. As demonstrated by the KIE (k_H/k_D = 4 at 115 °C), the rate-limiting step of methane oxidation is H atom abstraction. DFT calculations confirm the formation of the

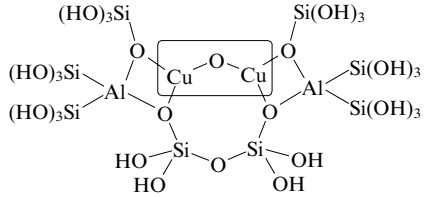
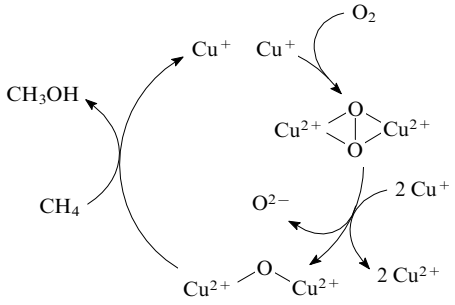


Figure 4. Structure of the active oxidant (α-O_{Cu}) on the CuZSM-5 zeolite on the basis of spectral data and DFT calculations.[269]

$[Cu-OH-Cu]^{2+}$ intermediate. The calculated activation energy (E_a) and KIE are in good agreement with experimental values.

The electronic structure of the complex with the $Cu_2^{II}O$ moiety enables the understanding of the reason for the high reactivity of this intermediate. Two low-lying partially filled molecular orbitals (HOMO) of the Cu^{II} atom considerably change in the course of reaction so that the complex structure becomes asymmetric. On the pathway to a transition state, one of the orbitals directed toward methane residing in the zeolite channel becomes more and more localized on the oxygen atom, like a *p* orbital. This leads to the formation of $Cu^{III}O^{\bullet}$, a metal oxyl intermediate with the reactivity comparable to that of a strong oxygen radical. Further studies[273] showed that the precursor of the reactive intermediate in the synthesis of methanol over CuZSM-5 is a μ-η^2:η^2-peroxo dicopper(II) species absorbing at 29 000 cm^{-1} and characterized by the corresponding Raman spectra. Two electrons required to break the peroxo bond are provided by spectator copper ions, which are not involved in the formation of α-sites. The $^{18}O_2$ experiments showed that one oxygen atom in this process is involved in the formation of the $Cu_2^{II}O$ core, whereas the second atom is incorporated into the zeolite lattice, presumably, it is bound to spectator copper sites (Scheme 5).

Scheme 5



The well-studied copper–oxygen model complexes (see above) oxidize only very weak C—H bonds (< 90 kcal mol^{-1}).[274] Some complexes can oxidize stronger C—H bonds as well; however, these complexes have been poorly studied so far. The bent $Cu_2^{II}O$ intermediates in CuZSM-5 are first comprehensively characterized sites capable of methane oxidation. It is worth noting that the structure of a $LCu_2^{II}O$ core was previously known or assumed for other copper complexes;[253] however, they had been poorly explored and, in addition, had limited reactivity.

V. Gold catalysis

Gold is more abundant in nature, more environmentally friendly and more readily available metal than the other noble metals used in catalysis. Being a soft Lewis acid, gold does not exhibit pronounced oxophilicity and is tolerant of dioxygen, water and other hydroxylic compounds. The functionalization of arene C—H bonds mediated by Au^{III} was discovered 80 years ago;[275] however, such reactions have been developed only in recent years.

Gold catalysts are, as a rule, highly active and can be used in extremely low concentrastions.[276, 277] Gold can be involved in catalysis as both Au^{I} or Au^{III} ions and free gold metal. Whereas massive gold is the most noble metal from the standpoint of stability to different reagents, gold nanoparticles are very reactive and selective in oxidative processes.[278] The ever increasing role of gold in catalysis and its ability to functionalize C—H bond[277] makes clear the significance of gold catalysis in solving the problem of methane hydroxylation. At the same time, it should be noted that, although nowadays one or two publications per day on gold-catalyzed processes appear in the literature,[276] the mechanism of these reactions and the nature of the reactive intermediates remain largely unclear.[279] The ability of gold to mediate anaerobic activation of C—H bonds[277] is beyond question; however, numerous data suggest that it can also activate O_2.[280, 281]

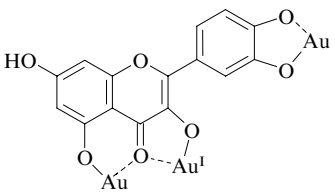
Aurophilic *Micrococcus luteus* bacteria in nature are able to accumulate gold from the environment and use it in their vital functions.[282] The recrystallization of gold around the bacteria, as well as the discovered effect of colloid and ionic gold on their cell respiration, transmembrane electrochemical potential and the ATPase activity, prove that gold is involved in the respiratory chains in bacteria, undergoing redox transformations.[282, 283]

In 1995, the so-called Au-protein was isolated from goldphilic bacteria *M. luteus* and characterized. This protein is a specific membrane-bound NADH oxidase with a molecular weight on the order of 600 kDa.[284] This protein contains three gold atoms and accounts for ~12% of the total protein fraction of membranes. According to spectral data, the Au-protein is a flavoproteid; however, unlike the known membrane-bound NADH oxidases, Au-protein uses flavonoid (rutin) as the second organic cofactor.[285, 286] The latter directly interacts with gold, changing the redox state of the protein.

It has been later found[287] that methane modifies the NADH oxidase activity of Au-protein. It has been demonstrated that gold forms a new active site in the protein and determines the character of its interaction with methane, favouring the involvement of methane in the redox cycle of this enzyme. It is worth noting that Au-protein is the first isolated enzyme in which the active site contains such a heavy metal as gold. Gas chromatography and isotope dilution of $^{14}CH_4$ with common methane[288, 289] have provided evidence that this enzyme efficiently catalyzes the formation of methanol from methane ($\sim 2 \times 10^3$ catalytic cycles per protein molecule) in an aqueous buffer solution (pH 8.0) at ambient temperature and pressure. Presumably, goldphilic bacteria use methane as an extra source of carbon and energy when sources of more easily digestible organic compounds are scarce. As is known, *M. luteus* usually dwell in silty soil and bottom sediments of reservoirs in the areas of gold mining, where methane is produced in the course of anaerobic methanogenesis processes (see Section II.1).

In 2004, the first functional biomimetic model of the active site of Au-protein was designed on the basis of the Au–rutin complex obtained in solution. The model mimicked the main function of the protein, *i.e.*, NADH-dependent methane oxidation to methanol.[290] The activity of the model system was about one-quarter of the Au-protein activity. In the absence of rutin, $AuCl_4$ also catalyzes the oxidation of NADH, which is accelerated in the presence of methane. However, this system works in an aqueous medium at pH 5.5–6.0 and at considerably higher concentrations of gold ions. The nearest methane homologues — ethane and propane — are oxidized more readily than methane, to produce, respectively ethanol and propan-2-ol.

It has been shown[291] that, among many known bioflavonoids, only quercetin can substitute for rutin as a ligand at the gold atom without noticeable loss of activity. In both cases, the process appears to be the NADH-dependent methane oxidation, and two moles of NADH is consumed per mole of the resultant methanol. According to DFT calculations,[291, 292] a trigold complex with rutin or quercetin has a structure simplistically represented by formula **18**; note that the omitted disaccharide residue protects the binuclear site in the complex.



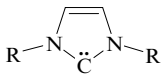
18

This is consistent with experimental data indicative of the high stability of the Au–rutin complex. Indeed, the catalytic activity of the Au–rutin complex persists for several weeks, whereas the Au–quercetin complex loses its activity within 3–4 h. As follows from formula **18**, one of the three gold atoms is chelated by a pyrocatechol moiety while the other two gold atoms form a binuclear site on coordination to the dinucleating ligand composed of two hydroxyl and one carbonyl oxygen atoms. The binuclear site can be envisioned as composed of Au^IAu^{III} or $Au^{II}Au^{II}$ complexes, both complexes being coordinatively unsaturated, which is necessary for activation of substrates and stabilization of resultant intermediates. The activity of rutin and quercetin as ligands is likely associated with their structure, which ensures conjugation between the binuclear site and the distant gold atom.

The electronic configuration of atom $Au^{III}(d^8)$ is analogous to that of Pt^{II} atom, which can activate methane in aqueous media under relatively mild conditions to form the $Pt^{II}-CH_3$ fragment (see above). At the same time, the electronic configuration of $Au^I(d^{10})$ corresponds to that of Pt^0, and both metals also activate methane, even if under more severe conditions, *i.e.*, more weakly. In this context, before proceeding to the mechanism of methane hydroxylation on Au-protein and its models, it is expedient to consider available data on functionalization of C–H bonds by gold complexes.

Research[293] specifically aimed at comparing the enzymatic and chemical alkane oxidations discovered an H_2O_2-based catalytic system containing Au^{III} and Au^I ions. It catalyzed oxidation in an acetonitrile solution at 75 °C (520 turnovers in 144 h), and major products were alkyl hydroperoxides. There was also reported the $NaAuCl_4$-catalyzed oxidation (TON = 10) of octane to octyl alcohol by air oxygen at room temperature in the presence of Zn in AcOH as the reducing agent and methyl viologen as the electron carrier.[293]

Gold(I)-catalyzed reactions of carbene and nitrene insertion into aliphatic C–H bonds are of great interest. With the use of the $LAu^ICl-NaBAr_4$ catalytic system [L is N-heterocyclic ligand **19**, Ar = 3,5-$(CF_3)_2C_6H_3$], the insertion of the $:CH_2CO_2Et$ carbene, from ethyl diazoacetate, into primary or tertiary C–H bonds of alkanes has been achieved.[294]



19

R = 2,6-$Pr^i_2C_6H_3$, Mes, 1-Ad (Ad is adamantyl), Bu^t.

In the reaction with 2,3-dimethylbutane, the high selectivity of the attack at primary C–H bonds as compared with tertiary bonds is observed. It is worth noting that, in the reaction mediated by an analogous copper complex, the selectivity is quite opposite: the reaction mainly yields the product of functionalization at tertiary bonds. The active catalyst in a gold-based system is an Au^I cationic complex, which also catalyzes nitrene transfer from corresponding azides.[295] In the case of toluene and PhI=NTs (an analogue of iodosobenzene PhIO, frequently used in synthesis of ferryl oxo complexes $Fe^{IV}=O$), the reaction occurs exclusively at the benzyl position.[296] This method is used for the intermolecular and intramolecular amination of aliphatic and aromatic C–H bonds.[297] The Au^I-catalyzed insertion of carbenes and nitrenes into sp^3 C–H bonds is

observed in many intramolecular reactions involving the reactive intermediate, Au^{I} carbenoid.[298] This mechanism is supported by the isotope label method and DFT calculations.[298]

An examination of similar reactions shows that, in many cases, the electronic structures of intermediates correspond better to a gold-stabilized carbocation than to carbene.[279] This situation somewhat resembles relations between electronic isomers $Fe^{IV}=O$ and $Fe^{III}-O^{\bullet}$ (see Section III.3). The author of the recent review[279] arrives at the conclusion that 'depending on the substrate and the ligand, as with the other transition metals, a continuum of intermediates ranging from gold-stabilized carbenes to gold-coordinated carbocations can be involved'. The facile Au^{I}-mediated carbene and nitrene transfer to aliphatic sp^3 C–H bonds suggests that a similar process is also possible for oxene. Indeed, the reactions of Au with N_2O and O_2 can yield AuO^- and $OAuO^-$, respectively.[280,281]

Recently, the terminal Au=O complex $K_{15}H_2[Au(O)(OH_2)P_2W_{18}O_{68}]\cdot 25\,H_2O$, which models redox-active metal oxide surfaces, has been synthesized by the reaction of $AuCl_3$ with the corresponding metal oxide cluster ligand and comprehensively characterized.[299] The $Au^{III}(d^8)$ atom is in an octahedral environment composed of equatorial polytungstate ligands and axial oxo and *trans*-aqua ligands. The complex has a very short Au–O distance (~1.76 Å) corresponding to a covalent bond similar (with the difference between the covalent metal atom radii taken into account) to the $Fe^{IV}=O$ bond (1.65 Å, see Section III). However, no evidence of gold-stabilized O atom transfer to the C–H bond has been found so far.

With regard to the aforesaid, it is likely that gold oxo complexes can be obtained through gold-mediated O_2 activation in the presence of NADH and protons, analogously to the recently described formation of $Fe^{IV}=O$ and $Fe^{III}-OOH$ complexes.[300] The oxidation of methane to methanol with the use of supported gold has been described;[278] however, its mechanism is unclear. Gold nanoparticles catalyze the oxidation of alkanes with dioxygen in the presence of a reducing agent.[301] Homogeneous selective methane oxidation in the Au–rutin system is possible, presumably owing to the formation of polynuclear Au–bioflavonoid complexes in solution. This is supported by the fact that the supernatant fluid formed after centrifuging nanoparticles in the Au–rutin system[302] is considerably more active in the NADH oxidation reaction than the sediment of nanoparticles. Moreover, this activity is one order of magnitude higher than the activity of the previously studied Au–bioflavonoid systems.[291] Although the exact nature of active catalytic sites in such systems is unknown and the mechanism of this process is not clear, the high efficiency of methane oxidation catalyzed by them deserves further research.

VI. Conclusions

The direct selective oxidation of methane to methanol by dioxygen is described by overall equation (11):

$$2\,CH_4 + O_2 \longrightarrow 2\,CH_3OH. \qquad (11)$$

Equation (11) corresponds to the dioxygenase mechanism and, formally, to anaerobic oxidation. At low temperatures in the absence of C–H bond activation, this pathway cannot be realized not only for methane but also for most alkanes because of their inertness. In the course of evolution, another mechanism, monooxygenase one, was found. It is described by Eqn (12):

$$CH_4 + O_2 + AH_2 \longrightarrow CH_3OH + H_2O + A, \qquad (12)$$

where AH_2 is reducing agent.

According to Eqn (12), methane can be oxidized to methanol if this reaction is coupled to the oxidation of a readily oxidizable substrate (AH_2), which is, in essence, an energy carrier. The reductive O_2 oxidation is accomplished by the active sites of methane monooxygenases containing iron or copper atoms. In the broad sense, any compound with an appropriate redox potential or cathode electrons can be used as an energy carrier.

An important feature of oxygenase enzyme systems is a spatial separation of the methane oxidation and physiological reductant (NADH or other) oxidation processes, which implies the existence of channels for supplying electrons and protons to the active site. The experience of Nature shows that the direct selective methane oxidation with dioxygen requires energy input [see reaction (12)]. The energy necessary for methane oxidation accumulates in the catalytic cycle at the stages of electron transfer to the metal site and then to oxygen. The reductive dioxygen activation on the metal site generates an energy-intensive short-lived intermediate capable of abstracting an H atom from methane. Studies of haem enzyme cytochrome P450 and its models have shown that such an intermediate is a high-valence iron oxo complex frequently referred to as ferryl intermediate. As follows from the data covered in this review, similar intermediates have also been discovered or suggested for non-haem and copper-containing oxygenases and some of their models. They have high reactivity comparable with that of free oxygen radicals. With certain reservations, the active intermediate of monooxygenases can be treated as the metal-coordinated O atom, the free one is known to be an active biradical. The latent character of such an intermediate allows calling it 'wolf in sheep's clothing'.

The discovery of homogeneous alkane activation by metal complexes in the late 1960s was the starting point for the emergence of a new field of catalysis, which has been rapidly developed up to now. Although much effort has been made to practically use the available information for design of the direct methane oxidation process, the suggested catalytic systems have disadvantages (corrosive media, relatively high temperatures, formation of by-products) and still cannot be commercially used. By their character, these systems are not so much biomimetic as chemical. However, not unsuccessful attempts are made to improve these systems (see, *e.g.*, Refs 302 and 303). The occurrence in nature of anaerobic methane oxidation, whose chemical model is the catalysis under consideration, clearly shows that similar processes can occur in an aqueous medium under common conditions and, thus, indicates the direction of further development of such systems. Studies of biological anaerobic oxidation of alkanes are still at an early stage, and it is hoped that the progress in this field will stimulate the design of more adequate chemical models.

In some respect, systems employing O_2 activation are believed to be more promising, first, because of favourable thermodynamics and, second, since they lead directly to methanol. The past decades have witnessed great advances in the study of cytochrome P450 and non-haem oxygenases,

as well as in their chemical modelling. Some of these models are already being put into practice. Despite an almost 30-year successful study of sMMO, efficient models of this enzyme have not been designed, presumably because of its complex structure. High expectations are associated with the recent discovery of methane oxidation with hydrogen peroxide catalyzed by binuclear N-bridged iron phthalocyanine complexes. This system is sufficiently active to directly oxidize methane, but has low selectivity and leads to at least three products: methanol, formaldehyde and formic acid, with predominance of the latter. However, its selectivity can be enhanced since there are many variable parameters. In addition, the selective stoichiometric oxidation of methane to methanol on iron-containing zeolites has the potential to transform to a catalytic process (for the prospects of this reaction, see Refs 248 and 304).

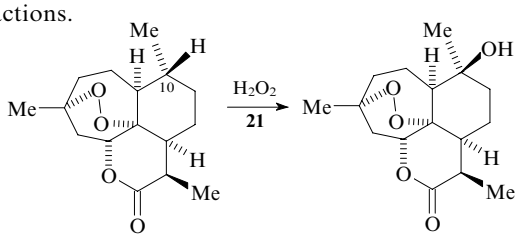
Even higher expectations are associated with copper-based model systems, which are still very small in number. Long-term efforts at elucidating the pMMO structure began to bear fruit, and it is now beyond question that pMMO has a binuclear Cu site and an ancillary copper ion, which is located nearby and serves for additional activation of the dicopper site. These findings are in consonance with the determination of the binuclear structure and mechanism of active sites of methane oxidation to methanol with dioxygen on copper-containing zeolites. Here, as in the case of pMMO, the process involves ancillary copper ions that do not belong to the binuclear site. The development of model chemical systems of copper-mediated methane oxidation can be expected in the near future, since complexes with a similar structure were synthesized but never tested (and presumably not suggested) as pMMO models.

Gold catalysis has recently become a burgeoning area of research. In the atomic, molecular and nanosized states, this formerly noble metal (*i.e.*, not reacting with any of chemicals) turned out to be an excellent and universal catalyst. The recently discovered ability of aurophilic bacteria to oxidize methane and the isolation of the active Au-protein from these cultures are of great interest. First chemical models of such sites can be very promising; however, it is clear that a lot of work lies ahead. The similarity between the geometric structures of the putative active sites for gold and copper immediately catches the eye. The similarity in the electronic structure of these metals suggests synergism in the development of model systems on their basis. The possibility of design of similar silver-based chemical models is also worthy of attention.

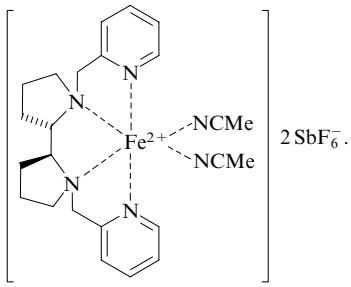
The problem of creation of an efficient catalyst of selective methane oxidation to methanol involves several challenges, and two of them — the catalyst activity and selectivity — head the list. Nowadays, there are enough examples of catalysts with potent sites capable of breaking the strong C—H bond in methane and of oxidizing it, sometimes even to CO_2.[305–307] The problem of selectivity seems to be more complicated. Indeed, beside the methane oxidation on metal-loaded zeolites and recently discovered systems based on biomimetic gold complexes in water, any efficient models of selective catalytic methane oxidation are still lacking.

However, there is encouraging progress in the related field. Works on modelling oxygenases laid the foundation for the development of preparative methods of selective oxidation of unactivated C—H and C=C bonds in complicated multifunctional molecules. This can be exemplified by the unprecedented oxidation of a very complex and rather labile molecule of artemisinin (**20**) — an antimalarial drug isolated from a herb employed in Chinese traditional medicine.

The one-stage oxidation of **20** with an inexpensive oxidant — hydrogen peroxide — catalyzed by biomimetic iron-based catalyst **21** similar to those discussed in this review affords the pure target monohydroxylated product in good yield with retention of stereochemistry and labile functionality and does not require the introduction of protecting or activating groups into the molecule.[308] This reaction, undoubtedly, enriched the arsenal of organic reactions.



20 (54%)



It should be remembered that the problem of methane oxidation to methanol is part of the general problem of tailored selective oxidation of unactivated C—H bonds. Inasmuch as the latter has been partially solved for some organic compounds with the use of the biomimetic approach, there are no doubts that, in this way, the solution for methane will also be found soon.[309, 310]

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