The role of metal-oxygen intermediates in biological and chemical monooxygenation of alkanes

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The role of metal-peroxo, -hydroperoxo, and -oxo intermediates in activation of O_2 and transfer of an oxygen atom to the C—H bond in biocatalysis by heme and non-heme monooxygenases and biomimetic oxidation of alkanes is reviewed.

Key words: cytochrome P450, methane monooxygenase, mechanism, metal-oxygen intermediates, monooxygenation of alkanes, hydroxylation of alkanes, biomimetic catalysis, ferryl, oxygen transfer, iron complexes.

1. Introduction

The interest in enzymes is evoked, on the one hand, by the desire to understand principles of biocatalysis and, on the other hand, by the search for more organized chemical processes similar to biological processes, which is the subject of biomimetic chemistry. A challenging problem in this area is the use of the thermodynamic potential of dioxygen by the kinetically controlled way for the directed oxidation of organic compounds as it occurs in living systems. Practically and theoretically important processes of alkane oxidation in traditional chemistry are difficult to control (non-selective) and require drastic conditions to occur.

At the same time, rather perfect (well organized) catalytic systems, *viz.*, monooxygenases, exist in Nature for the controlled oxidation of alkanes and other compounds. Most monooxygenases are metal-enzymes containing transition metal ions, predominantly iron or copper. Their role is reduced to the activation of molecular oxygen and a decrease in the kinetic barrier to its reaction with hydrocarbons due to the formation of reactive metal-oxygen intermediates. Understanding of the mechanism of dioxygen activation by monooxygenases will allow one to elucidate the general principles of hydrocarbon oxidation catalyzed by transition metal compounds and to develop theoretical concepts for biomimetic catalysis of the oxidation of alkanes and other compounds.

All monooxygenases form two products involving O_2, *vz.*, the monooxygenated substrate (SO) and a water molecule

$$S + O_2 + 2e^- + 2H^+ \longrightarrow SO + H_2O. \qquad (1)$$

Here, coupled oxidation of the difficultly oxidizable substrate (alkane) (S) and readily oxidizable natural reducing agent, NADH* or NADPH, occurs.

According to the most common view, this process is the transfer of the oxygen atom from an active metal-oxygen intermediate, formed upon reductive activation of O_2 by the metal complex M, to a substrate

$$M \longrightarrow MO_2 \longrightarrow M(O_2^{2-}) \longrightarrow M(O) \xrightarrow{S} SO + M$$

The following points should be understood first to develop efficient biomimetic catalysts for alkane monooxygenation:

1) what is the nature of the metal-oxygen intermediates and how does the cleavage of the O—O bond occur on going from the dioxygen intermediate to the monooxygen one?

2) which of these intermediates interact with alkanes and what is the mechanism of the O atom insertion into the C—H bond?

3) what specific features of the enzyme structure or the mechanism of its action determine high selectivity of biocatalytic oxidation involving monooxygenases?

4) is it generally possible, based on the known mechanism and principles of monooxygenase functioning, to create simple chemical analogs which are not inferior, however, to enzymes in the efficiency and selectivity of oxidation?

As is shown below, the answers to many of these questions can be obtained using data on the structure of active centers of several monooxygenases and the kinetics of enzymatic oxidation of alkanes, newest spectral

* NADH is reduced nicotinamide adenine dinucleotide, NADHP is reduced nicotinamide adenine dinucleotide phosphate.

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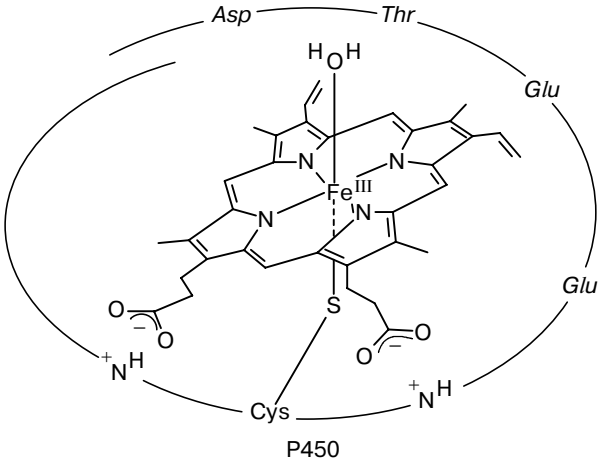
methods and quantum-chemical calculations for the understanding of the structures and reactivities of active intermediates along with attempts of chemical modeling of particular stages of the biological oxidation of alkanes in simple systems including metal complexes with the known structures.

2. Monooxygenases and mechanisms of their action

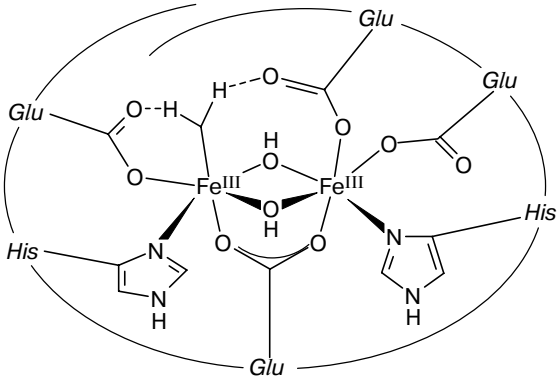
Two types of monooxygenases are the most studied to the date, *viz.*, the heme monooxygenase, cytochrome P450 (P450), and the non-heme enzyme, methane monooxygenase (MMO)*. Cytochrome P450 [1,2] was found in a wide range of organisms from bacteria to mammals where it performs various functions; MMO is present in methanotrophic microorganisms for which methane is a single source of carbon and energy. These two enzymes exist in both the soluble and membrane-bound state and, along with the hydroxylation of alkanes and other compounds containing the C—H bond, perform diverse oxidation reactions (dehydrogenation of saturated compounds, epoxidation of alkenes, formation of *S*- and *N*-oxides, *etc.*). However, alkane hydroxylation is the property uniquely inherent in these monooxygenases. Despite P450 and MMO perform the same reactions, their active centers (Schemes 1 and 2) have different structures, which suggests possible distinctions in the mechanisms of their action. According to Eq. (1), both enzymes require a reducing agent, which, in the case of P450, can represent a cofactor of the enzyme itself or be a component of a multienzyme complex. In the case of MMO, the hydroxylase component containing the binuclear active center (Scheme 2) always forms a multienzyme complex together with reductase and a coupling (regulatory) protein **B**, which is small in size but is very significant for catalysis.

Scheme 1



* Terms P450 and MMO are used henceforth, in most cases, as singulars, although numerous isozymes P450 are available and several MMO from various bacterial sources are known.

Scheme 2



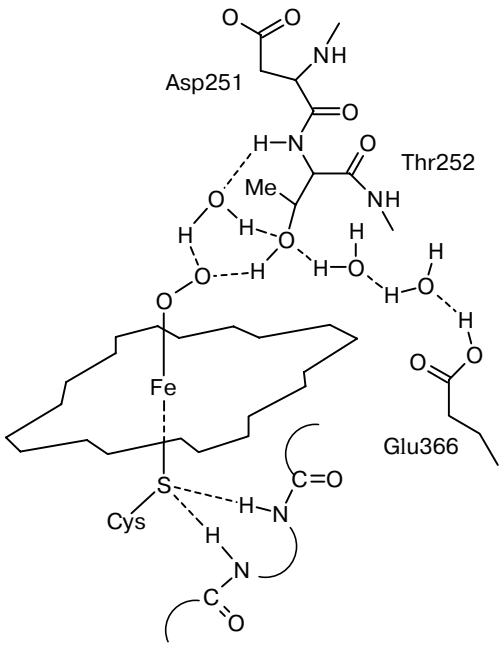
MMO

2.1. Cytochrome P450

As follows from spectroscopic and X-ray diffraction data,[3,4] the active center of P450 contains the heme cofactor, Fe (protoporphyrin-IX) (see Scheme 1), which is bound to the protein by salt bridges and hydrogen bonds through the propionate groups and due to the coordination to iron of the thiolate group of cysteine at the proximal side of the porphyrin ring. The protein-incorporated octahedral iron complex is formed in which the porphyrin ligand occupies four equatorial coordination sites, and the fifth (axial) site is occupied by thiolate. The sixth (also axial) coordination site at the distal side of the porphyrin has in its environment predominantly lipophilic amino acid residues, which form the so-called hydrophobic pocket for substrate binding and is the stage where the catalytic action takes place. Elimination of the water molecule which occupies the sixth coordination site in the initial ferri state of the complex occurs upon binding of an alkane or other substrate thus liberating this coordination site for subsequent binding of dioxygen following reduction of iron to the ferro state. The latter forms a strong complex with CO. The UV spectrum of this complex contains an intense band at λ = 450 nm due to which the cytochrome was named "pigment 450." Hydrophobic binding of the substrate results in the transition of the iron to the high-spin state, increases the redox potential of the complex, and facilitates transfer of an electron from the reducing agent to form Fe^{II}, which interacts with O_2 and affords the dioxygen complex similar to the dioxygen complex of hemoglobin. At low temperatures, this complex is relatively stable and can be observed by spectral methods.[5] The transfer of the second electron to it is accompanied by the formation of oxidation products. No transient stages in this complicated process were isolated to date in the case of the enzyme itself because the rates of conversions of intermediates are much higher than the rates of their formation and, hence, they cannot be accumulated in concentrations sufficient for their identification (however, see below).

Analysis of the crystal structure of P450 indicates that yet another hydrophobic region, the so-called cysteine pocket, exists at the proximal side of the heme. Conformational changes in the adjacent α-coil region of the polypeptide chain control the redox properties of the heme-thiolate center through a system of hydrogen bonds and a coordinated thiolate (Scheme 3).[6] A rather perfect structural model of P450 with two hydrophobic cavities at both sides of the heme and the thiolate ligand on iron has recently been synthesized where the dioxygen complex is stabilized by additional hydrogen binding.[7] This model binds reversibly CO and O_2, whose spectroscopic parameters are very close to those of the corresponding derivatives of P450.

Scheme 3



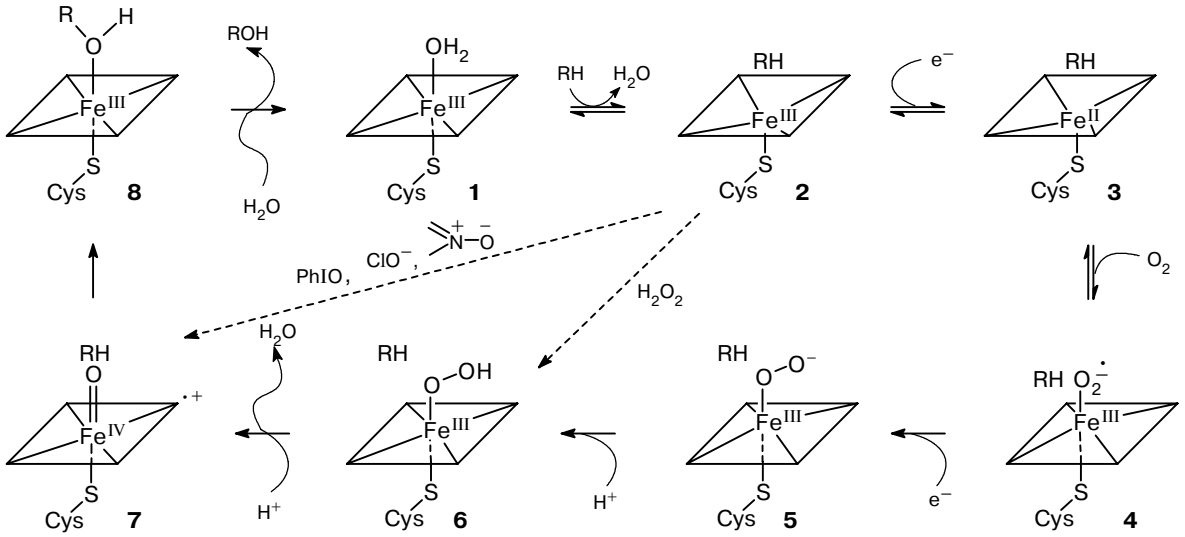
Based on extensive and keen insight over the recent 30 years, we can present the catalytic cycle of P450 with a high reliability (Scheme 4). Intermediates **2**—**5** and **7** were isolated and characterized by various spectral methods and X-ray diffraction analysis. The existence of hydroperoxide intermediate **6** follows from quantum-chemical calculations, experiments with a mutant enzyme P450, and crystallographic data (see below). The key oxidating intermediate **7** is formally $PFe^{V}=O$ but it is better described as the $P^{+\cdot}Fe^{IV}=O$ species with iron in the oxidation state IV and porphyrin radical cation ($P^{+\cdot}$). Of three dioxygen intermediates of the catalytic cycle of P450, the most data were obtained for the $Fe^{II}O_2$ intermediate **4**, whose structure was characterized by various spectral methods, including EXAFS (Extended X-ray Absorption Fine Structure), and confirmed by X-ray diffraction data for the corresponding model heme-thiolate complexes. The fact that the transfer of the second electron in the stage determining the rate of the whole process results primarily in peroxo complex **5** follows from the UV spectrum of this intermediate on mutant P450 in which the proton transfer is partially blocked by the replacement of certain amino acid residues. There is good agreement between the spectra of intermediates $Fe^{II}O_2$ and $Fe^{II}O_2^-$ calculated using quantum-chemical DFT (Density Functional Theory) methods[8] and experimental ones.[9] Subsequent stages were proposed by analogy with the better studied, related heme enzymes using hydrogen peroxide as a substrate (peroxidase, catalase) or synthetic model systems and as a result of stringent theoretical calculations.[8]

Peroxidases perform one-electron oxidation of compounds which are much more reactive than alkanes. Unlike P450, they have histidine as a proximal ligand instead of thiolate and use peroxides as an oxidant instead of O_2. The active oxidating intermediate of peroxidases was isolated and characterized as the high-valence oxenoid* iron complex with the $P^{+\cdot}Fe^{IV}=O$ structure and named Compound I or "ferryl intermediate." It is assumed that the heterolytic cleavage of hydrogen peroxide with the formation of a similar intermediate and the water molecule mimics the corresponding stage involving P450. Studies with isotope-enriched O_2 established that the oxygen atom directly bound to the heme iron of P450 is transferred to the substrate and the terminal O atom enters the water molecule that formed.[8] It follows from calculations that the terminal O atom of peroxo intermediate **5** in P450 is doubly protonated, which facilitates the heterolytic cleavage of the O—O bond to form water and the ferryl intermediate **7**. This concept is favored by the fact that, in the absence of NAD(P)H, P450 catalyzes oxidation of alkanes by peroxides in a "peroxide shunt" pathway (Scheme 4, dotted arrows). Moreover, oxygen atom donors, such as iodosobenzene, PhIO, or hypochlorite, ClO^-, can also be used in shunted systems, most likely, due to the direct formation of the ferryl intermediate by the transfer of the O atom from the oxidant (Scheme 4, dotted arrows). Attempts to isolate ferryl intermediate **7** in the natural cycle of P450 failed, whereas its spectral observation is possible for the system shunted by *m*-chloroperbenzoic acid.

The intermediates shown in Scheme 4 were identified in model systems using synthetic analogs, especially iron *meso*-tetraarylporphyrin complexes. The first synthetic system modeling the chemical behavior of P450 was iron tetraphenylporphyrinate, Fe^{III}(tpp)Cl, which effected stereospecific epoxidation of alkenes and hydroxylation of hydrocarbons in the presence of iodosobenzene. The active intermediate in this system is the ferryl complex $P^{+\cdot}Fe^{IV}=O$, the structure of which was assigned from spectroscopic data. It was shown that this species can be obtained from the preliminarily synthe-

* Formed by the addition of the O atom (oxene) to FeP.

Scheme 4



sized peroxo complex by the heterolytic cleavage of its O—O bonds using O^{2-} acceptors, such as protons[10] or acyl cations.[11]

The complete catalytic cycle of P450 during alkane oxidation with molecular oxygen was modeled in the electrochemical system in the presence of a synthetic iron porphyrin complex and acetic anhydride (as a donor of Ac^+).[11]

The necessary stage in molecular oxygen activation is the controlled transfer of a proton to it, which is problematic in the hydrophobic active site of P450. Studies with the use of directed mutagenesis showed that the polar amino acid residues of the distal region of the heme participate, most likely, in proton transfer to the oxygen of the peroxo complex resulting in an intermediate which hydroxylates the substrate.[9] This assumption has later been confirmed by X-ray diffraction analysis (see below). It is considered that the strongly nucleophilic thiolate axial ligand is crucial for the heterolytic cleavage of the O—O bond by donating of the electron density to this bond.[12] The concerted action of the axial thiolate and protons in the heterolytic cleavage of the O—O bond follows the so-called push-pull mechanism.

The structures of intermediates **3** (ferro), **4** (oxy), and **7** (oxo) (see Scheme 4) have recently been established and the catalytic cycle of P450 has been monitored at the atomic resolution using special technique of trapping transient intermediates and cryocrystallography.[13] In the binding of dioxygen to ferro-P450, slight but important changes in the protein environment near the active center result in the formation of a proton shuttle (see Scheme 3). One atom of the oxygen molecule is linked with iron and the molecule is fixed in a certain position by hydrogen bonds involving hydroxyls of Thr and water. The X-ray irradiation of oxy-P450 crystals at a wavelength of 1.5 Å at 100 K for 3 h results in the formation of oxo-P450 due to transfer of the second electron formed upon water radiolysis to iron. The Fe—O distance in oxo-P450 was equal to 1.65 Å in agreement with the ferryl nature of this intermediate.[14] A water molecule was observed near the ferryl oxygen. Perhaps, this water molecule is the "leaving" H_2O formed from the distal oxygen upon the cleavage of the O—O bond. In accord to what has been assumed, the thiolate ligand retained in this intermediate, and the Fe—S distance was close to that observed in oxy-P450. Upon flash thawing, the O atom is stereospecifically transferred to the substrate to form the known ferri-P450. Thus, it was crystallographically confirmed that the transfer of the second electron to iron results in the cleavage of the O—O bond and formation of the ferryl intermediate. Protons necessary for this process are delivered to the hydrophobic active center of P450 through the system of hydrogen bonds by the shuttle mechanism (see Scheme 3) involving amino acid residues Thr and Asp and several ordered water molecules. Evidently, the specific organization of amino acids and bound water molecules that participate in the O—O bond cleavage can differ for P450 isozymes. Some structural proofs for the formation of the hydroperoxide intermediate were also obtained.[13]

The study of the heme-thiolate model complexes demonstrated that the thiolate ligand is the reason for all unusual spectral characteristics of P450 and also, which is especially significant, increases the rate of O—O bond cleavage in these complexes and favors its heterolytic, rather than homolytic, cleavage.[15] Iron porphyrin with the organized hydrophobic cavity at the distal side and thiolate bound to the porphyrin ligand has recently been proposed[16] as a model of the active center of P450. This complex possesses a remarkable stability, it retains its structure, including the bound thiolate ligand, during catalytic alkane oxidation in

benzene, whose polarity is close to that of the environment of the active center of P450. It has been shown that the thiolate ligand accelerates significantly the O—O bond cleavage in peroxy acids and also, which is essential, favors the heterolysis of this bond even in a strongly non-polar medium without involvement of an additional acid or base.[16] The ferryl intermediate formed in this model system possesses high electrophilicity and can hydroxylate alkanes and epoxidize alkenes with comparable rates, similarly to the active intermediate of P450. The rate constants for the heterolytic cleavage of the O—O bond and hydrocarbon oxidation for models with different axial ligands follow the series: thiolate > imidazole* ≫ chloride anion.[16] These experiments convincingly confirmed the role of the thiolate ligand of the heme for P450 functioning.

In the presence of the thiolate ligand, ferryl attacks the C—H bond preferably rather than adds to unsaturated systems,[15] which is usually related to an increase in the contribution of the structure with the coordinated thiyl radical: $P^{+\cdot}Fe^{IV}=O(RS^{-}) \rightarrow PFe^{IV}—O^{\cdot}\ (RS^{\cdot})$.[17] In fact, the DFT calculations showed that RS^{-}, to a greater extent than Im or Cl^{-}, (a) stabilizes the $Fe^{V}=O$ fragment compared to $Fe^{IV}=O$, (b) favors the heterolytic, rather than homolytic, cleavage of the O—O bond, and (c) decreases the activation barrier to alkane hydroxylation.[18]

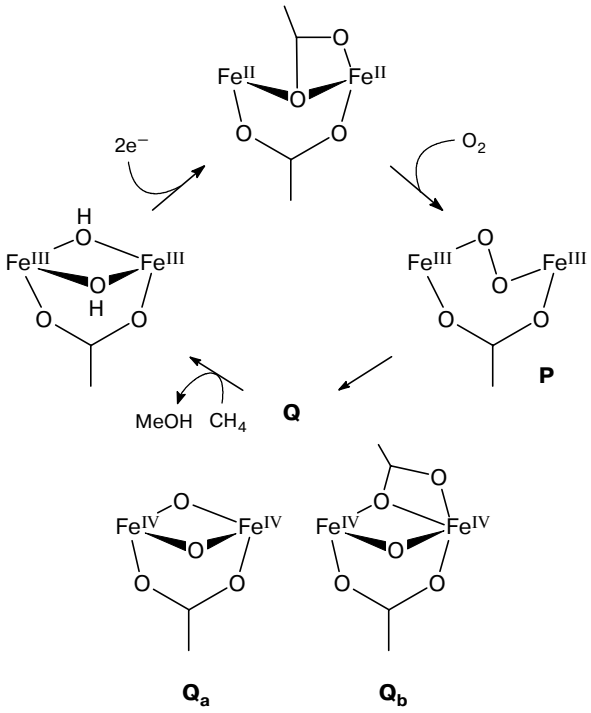
Thus, profound experimental studies on the enzyme and models and quantum-chemical calculations provided a rather plausible picture of dioxygen activation by heme monooxygenase P450 with the formation, due to the heterolytic cleavage of the O—O bond, of the unique heme-thiolate ferryl intermediate which transfers the O atom to the C—H bond of alkanes. These studies showed that P450 is a well-organized biocatalyst for the controlled oxidation of alkanes and other substrates and opened a new catalytic reaction in chemistry, *viz.*, monooxygenation of non-activated C—H bonds.

2.2. Methane monooxygenase

Soluble MMO from *Methylococcus capsulatus* (Bath) and *Methylosinus trichosporium* OB3b are most studied.[19—21] Both MMO have a similar rather flexible active center (see Scheme 2) containing two iron atoms bound to the protein through four carboxy groups of the glutamic acid residues and two imidazole rings of the histidine residues. During the catalytic cycle at least one of these carboxy groups remains as a bridge between the iron atoms, which is important, most likely, for their concerted functioning. In addition, several exogenic hydroxo or aqua ligands can be linked with iron. Some of these ligands along with the carboxy group form at most three bridges between the iron atoms. The X-ray structural data for various forms of ferri-MMO show that the carboxylate and hydroxo bridges remain unchanged, whereas OH, H_2O or carboxylate can represent the third bridge.[22,23] According to EXAFS, the two- and three-bridged forms are at equilibrium in a solution.[24] The distance between the iron atoms in all these forms varies from 3.0 to 3.4 Å. This indicates the capability of the binuclear iron cluster of tuning to the structure of various intermediates of the catalytic cycle. Unlike the heme iron in P450, which has only one coordination site for the formation of oxygen intermediates, in the case of MMO, at least four coordination sites occupied by exogenic ligands in the initial ferri state participate, most likely, in the catalytic process. As we show further, this abundance of labile coordination sites is possibly associated with the specific features of the bridging activation of O_2 in the active center of MMO. In ferro-MMO, both iron atoms become five-coordinate, which provides the possibility of the addition of the O_2 molecule to form a bridge between these iron atoms.[23]

The catalytic cycle of MMO (Scheme 5) resembles somewhat the catalytic cycle of P450 despite important distinctions. In the case of MMO, it was possible to detect and characterize the key intermediates **P** and **Q** in the native system due to their accumulation in a noticeable concentration before they react. However, their exact structure still remains the subject of numerous discussions. The hydroxylase component reduced by

Scheme 5



* Although peroxidase, in which imidazole of histidine is the axial ligand, forms the ferryl intermediate with two oxidative equivalents, it cannot, nevertheless, hydroxylate alkanes because of steric hindrances for the attack of the C—H bond by the O atom in this enzyme.

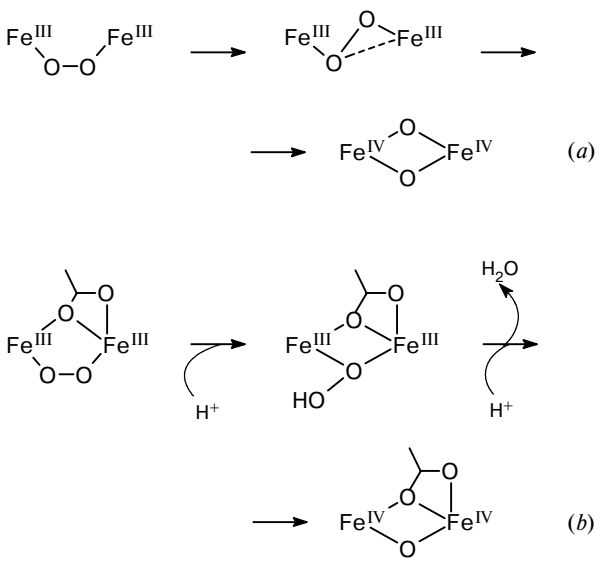
dithionite can perform the stoichiometric oxidation of methane by dioxygen (one cycle) in the absence of reductase.

The reaction of ferro-MMO with O_2 was studied by stopped-flow optical spectroscopy,[25,26] which showed that the first intermediate observed is diferriperoxide **P**, whose optical spectrum resembles those of the corresponding chemical analogs. The rate of this process is independent of the O_2 concentration in a wide interval. This may suggest the very fast and, in essence, irreversible formation of a dioxygen complex as a precursor of intermediate **P**, which, however, could not be identified. The Mössbauer spectrum of intermediate **P** confirmed that the constituent iron exists in the high-spin ferri state although with somewhat unusual characteristics, *viz.*, the isomeric shift $\delta = 0.66$ mm s^{-1} and the quadrupole splitting $\Delta E_Q = 1.55$ mm s^{-1}. Similar characteristics have later been obtained for a model binuclear μ-1,2-peroxide iron complex. The presence of only one quadrupole doublet in the Mössbauer spectrum of intermediate **P** indicates the symmetric arrangement of peroxide between the iron atoms. Compound **P** is spontaneously transformed into intermediate **Q**. The rate of this transformation is independent of the presence of methane, and the rate of the disappearance of **Q** is proportional to its concentration. It was thus concluded that this is **Q** that is the species that reacts with methane. The disappearance of **Q** in the reaction with methane is reliably detected from a decrease in the characteristic absorption. In the absence of the substrate, compound **Q** can be accumulated in concentrations sufficient for various spectral studies. The Mössbauer spectra of frozen solutions of intermediate **Q** indicate that the constituent iron exists in the high-spin Fe^{IV} state, and the iron atoms are antiferromagnetically coupled to form a symmetrical diamagnetic cluster $Fe^{IV}—O—Fe^{IV}$.[27] Analysis of EXAFS data for this intermediate revealed a relatively short Fe—O bond and an unusually short distance between the iron atoms.[27] The Fe—O bond length in intermediate **Q** (1.8 Å) is longer than the terminal Fe=O bonds in the porphyrin complexes of high-valence iron but is comparable with those of Fe—O in binuclear μ-oxo complexes containing the Fe—O—Fe fragment. A rather short distance between the iron atoms in intermediate **Q** suggested the presence of more than one oxygen bridge between these atoms. Two structures ($\mathbf{Q_a}$ and $\mathbf{Q_b}$), which agree with these data, are shown in Scheme 5,[28,29] and the former seems more preferential at the moment: first, model complexes with the $Fe_2(\mu\text{-}O_2)$ core were obtained,[28] and second, this structure is supported by recent theoretical calculations.[30]

The kinetic data indicate that all three components of MMO are important for catalysis. They possess high affinity to each other and form a multienzyme complex in which the Fe_2 cluster can undergo two-electron reduction. When the multienzyme complex of MMO is formed, the hydroxylase component is subjected to considerable conformational changes resulting in a change in its shape, as follows from the data from small-angle X-ray scattering.[31] Protein **B** (see above) plays the decisive role in the key stages: this accelerates 40-fold O_2 binding, the yield of the products increases from 40 to 80%, and the presence of reductase increases the yield to 100%. Protein **B** regulates the electron transfer from reductase to hydroxylase in such a way that it occurs only in the presence of substrates, and it increases the rate and changes the regioselectivity of alkane oxidation. Binding of protein **B** results in changes in some spectral characteristics of the reduced Fe_2 cluster, indicating possible changes in the coordination environment of the iron atoms.

Presently, two mechanisms of the $\mathbf{P} \rightarrow \mathbf{Q}$ transformation are assumed: they include either the homolytic (a),[30,32] or heterolytic (b)[19] cleavage of the O—O bond (Scheme 6). The former mechanism does not imply involvement of a proton and resembles that of O_2 activation with the Cu_2 cluster of tyrosinase. In this mechanism, the electrophilic iron ions function as the O^{2-} acceptor rather than protons. The latter mechanism requires double protonation of one O atom of the bridging peroxide and resembles the mechanism of O_2 activation by enzyme P450. Arguments in favor of the homolytic mechanism are mainly based on results of the corresponding theoretical calculations[30] and preparation of synthetic complexes with the $Fe_2(\mu\text{-}O)_2$ core, whose characteristics are close to those of intermediate Q.[28] The heterolytic mechanism is inferred from kinetic studies of MMO from *Methylosinus trichosporium* OB3b.[33] The effect of pH and account of proton consumption suggest that two protons are needed for O_2 fixation in the absence of a substrate: one proton is necessary for the formation of intermediate **P**, and another proton is

Scheme 6



needed for its transformation into intermediate **Q**.[33] However, other explanations of this effect are possible[30,34] (see below).

More detailed kinetic studies of MMO revealed new specific features of the mechanism of alkane hydroxylation.[25,26,33] First, these studies confirmed that intermediate **P** is preceded in the reaction of ferro-MMO with O_2 by one more dioxygen intermediate **P***, whose structure is yet unknown. Then, the activation of O_2 is sensitive to pH and deuteration of the solvent, which indicates involvement of protons in this stage. The water molecule in the coordination sphere of iron was assumed as the immediate donor of protons.[33] It is possible, however, that these effects are related to the influence of the pH on the H-bond network, which is directly involved in the catalytic process.[30,34] Methane exhibits some anomalies in the reaction with **Q**, *viz.*, the unusually high isotope effect (50—100), which is virtually absent from reactions with other alkanes, and the highest oxidation rate among alkanes, which is poorly consistent with the highest strength of its C—H bonds. It was assumed that the mechanism of the reaction of methane with intermediate **Q** differs from the mechanism for other alkanes and, perhaps, includes proton tunneling. On the other hand, the plot of the logarithm of the rate constant for the reaction of intermediate **Q** with methane *vs.* inverse temperature (the Arrhenius plot) is non-linear (it consists of two linear regions with an inflection point). This suggests, most likely, the two-stage mechanism of the reaction of methane with intermediate **Q** and a change in the limiting stage with the increase in temperature.[25,26] The absence of the isotope effect and standard temperature dependence of the rate of the reaction of other alkanes with intermediate **Q** suggest that in this case it is not the cleavage of the C—H bond that is the limiting stage but some other reaction, perhaps, substrate binding in the active center. The activation parameters for the **P** → **Q** transformation and for the reaction of **Q** with methane in the temperature range where the C—H bond cleavage is the limiting stage agree satisfactorily with DFT calculations.[30,34,35]

Quantum-chemical calculations using a hybrid DFT method and multiatomic models (up to 100 atoms) performed in recent years revealed important details in the structures of intermediates **P** and **Q** and their reactions.[30,34,35] Reliability of these *ab initio* methods was demonstrated by correct simulation of X-ray structures of the active centers of ferro- and ferri-MMO, including the peripheral H-bond networks.[34] The use of rather large models helped to identify the region of an increased electron density as a water molecule included into the network of H-bond, which has not earlier been recognized in the X-ray structure of ferro-MMO. It has been shown that this network plays a substantial role in the integration of the ferro-MMO structure and makes it rather strained, which is possibly necessary for further catalytic transformations. Moreover, the H-bond network is necessary for the stabilization of intermediates **P** and **Q**, and it is rearrangements in H bonding that control the distance between the iron atoms and the transformation of one intermediate into another. It turned out that the water molecule coordinated to the iron and incorporated into the H-bond network plays the key role in stabilization of the structures of intermediates **P** and **Q**.[34]

It was generally accepted that the $Fe_2N_5O_5$ coordination environment rich in nitrogeneous donors, as in the nonheme O_2 mediator hemerythrin, cannot provide O_2 activation by the cleavage of the O—O bond, as this occurs in the case of MMO non-heme hydroxylase with the $Fe_2N_2O_7$ environment rich in oxygen donors. However, membrane-bound oxygenases with the coordination environment of iron rich in nitrogeneous donors have recently been discovered.[36] It is worth mentioning that similar nonheme alkane monooxygenase from *Pseudomonas oleovorans* (AlkB), which is named sometimes ω-hydroxylase, has a binuclear active center, and catalyzes hydroxylation of *n*-alkanes C_5—C_{12} at the methyl group.[37] Since the stoichiometry of oxidation with ω-hydroxylase is the same as that for P450 and MMO, it is assumed that its active intermediate is also a ferryl derivative.[38] ω-Hydroxylase has an important structural distinction from MMO: the predomination of nitrogeneous donors in the coordination sphere of AlkB and the presence of the oxo bridge between the iron atoms[37] as in hemerythrin.

Thus, in recent years we have a substantial progress in understanding of such a wonderful invention of Nature as MMO, which selectively oxidizes the inert methane molecule to methanol under mild conditions. It turned out that, despite substantial distinctions in the structure of the active centers, both monooxygenases, P450 and MMO, have many common features in the mechanisms of O_2 activation and alkane oxidation, although, perhaps, certain peculiarities in the mechanism of methane oxidation remain to be elucidated. It became clear recently that the H-bond network involving polar amino acid residues and ordered water molecules plays a great role in functioning of both monooxygenases. The mechanism of P450 can be considered reliably proven, up to the observation of the catalytic cycle at atomic resolution, whereas much remains unclear in the case of MMO. The distinctions in the structures of the active centers result in different types of O_2 activation, which is terminal for P450 and bridging for MMO. Nevertheless, the characters of the intermediates of the catalytic cycles have much in common. The peroxo intermediate plays the great role in O_2 activation in both monooxygenases, and the ferryl fragment is the active oxidant in both cases.

2.3. Peroxo and hydroperoxo intermediates

Distinct identification of intermediates in the biological and chemical monooxygenation of alkanes and the study of their reactivity are of interest for both deep

insight into the mechanism of these processes and perfection of chemical model systems.

The disturbance of the normal way of proton transfer in the active center of P450 by directed mutagenesis (see above) both allowed the isolation of the peroxo intermediate and simultaneously resulted in the accumulation of the hydroperoxide intermediate, which followed from an increase in the ratio of epoxides to allylic alcohols upon alkene oxygenation.[39] These results suggested the presence of two electrophilic oxidants in the catalytic cycle of P450. One of them, hydroperoxide, is predominantly epoxidizing agent, and another oxidant, ferryl, is predominantly hydroxylating agent. Experiments with the same mutant showed that, in the absence of unsaturated compounds, the hydroperoxide intermediate also effects alkane hydroxylation.[40,41] Presumably, the hydroperoxide intermediate in P450 hydroxylates alkanes with the transfer of OH^+ instead of O, as in the case of ferryl.[40] The protonated alcohol that formed then undergoes rearrangements well-known in solvolytic processes competing with fast deprotonation. This explains the appearance of the rearrangement products in the oxidation of specially designed substrate probes (see below).

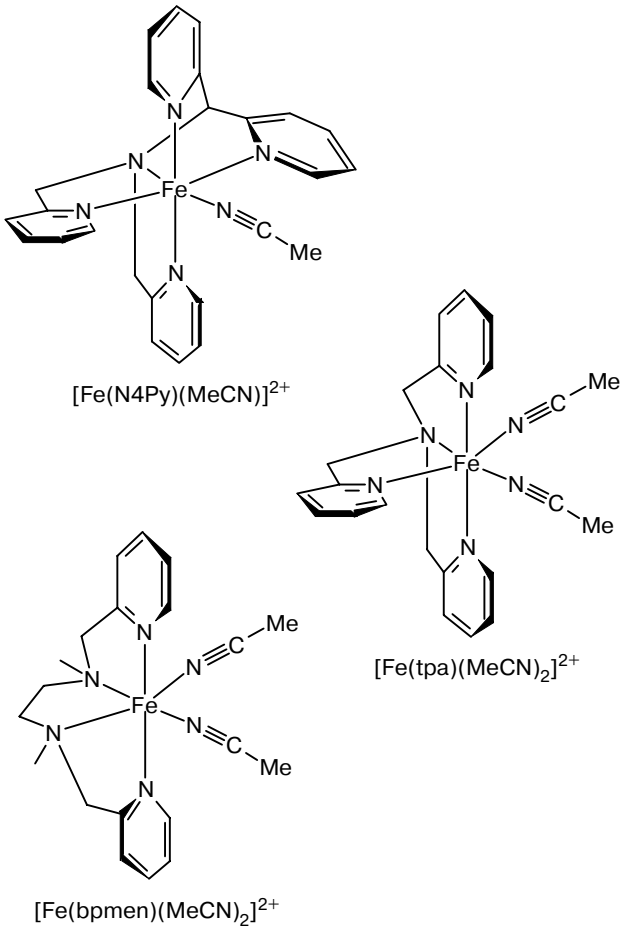
The peroxo intermediate is formed upon the transfer of an electron derived upon radiolysis to oxy-P450 in the frozen matrix.[42]

Peroxo complexes of ferriporphyrins can be obtained in aprotic solvents by the reaction $PFe^{II} + O_2^{\cdot -}$ or the reduction of the oxygen complexes $PFe^{II}O_2$[43] and have cyclic structures.[44,45] Axial ligands, including RS^- and, most likely, $O_2^{\cdot -}$, favor the formation of a more nucleophilic open form.[46–48] Although the reactivity of $PFe^{III}—OO^-$ depends on the nature of the axial ligands in the porphyrin,[46] these intermediates themselves do not react with alkanes under any conditions.[47] The nucleophilic character of the peroxo complexes is demonstrated by their acylation. In the reaction of $PFeO_2^-$ (P = tpp, tmp) with acetic anhydride or acetyl chloride the formation of $PFe^{III}OOAc$ was observed.[11]

The bridged peroxide intermediate of the binuclear center in MMO is well characterized by spectroscopy. Model complexes of this type were synthesized and characterized in solutions at low temperatures,[49] and for some of them X-ray structural data are available.[50–52] The bridged peroxo derivatives of binuclear iron complexes, like heme peroxo complexes, are nucleophiles and cannot themselves oxidize alkanes.

Several mononuclear hydroperoxide and alkyl peroxide low-spin iron complexes were synthesized.[53–55] The rate of the homolytic cleavage of the O—O bond in complexes of the $[Fe(bpy)_2(OOH)L](NO_3)_2$ type increases with the increase in the basicity of L.[55] The homolysis of Fe(tpa)—OOR (where tpa = tris(2-pyridylmethyl)amine) obtained and characterized at —40 °C affords the Fe^{IV}=O and RO$^{\cdot}$ intermediates. It has been shown that alkane oxidation in this system is associated with the involvement of the alkoxyl radical and, as is shown in experiments with *cis*- and *trans*-1,2-dimethylcyclohexanes, is not stereospecific.[54] However, it turned out that a short-lived intermediate Fe(tpa)—OOH with similar structure, which has also been obtained and characterized at −40 °C brings about stereospecific hydroxylation of *cis*- and *trans*-1,2-dimethylcyclohexanes at tertiary bonds.[54] The corresponding complex with the pentadentate nitrogen ligand, Fe(N4Py)—OOH, decomposes homolytically and performs non-stereospecific oxidation of alkanes.[56] The structures of the complexes with these ligands are shown in Scheme 7. It is most likely that the reason for the stereospecificity of Fe(tpa)—OOH is related to the presence of a labile coordination site on iron complexed with the tetradentate ligand tpa and a hydroperoxide.[54]

Scheme 7



Acylperoxo complexes represent analogs of hydroperoxo complexes and are formed in nature only in shunted systems involving peracids. Depending on the nature of the axial ligand, the $PFe^{III}—OOC(O)R$ complex obtained in a model system from *m*-chloroperbenzoic acid at −40 °C either performs alkane hydroxylation at this temperature[57] or serves as a pre-

cursor of ferryl. It is known that the direction and rate of the O—O bond cleavage in PFe^{III}—OOR or PFe^{III}—OOC(O)R is determined by the electron properties of the ligands linked with iron in enzymes or models.[12,58] Apparently, the ligands can influence the oxidizing ability and lifetime of the peroxide intermediate. The hydroperoxide itself can act as a hydroxylating intermediate if its oxidizing ability is sufficient for the reaction with alkane and the lifetime is rather long for the O transfer to occur prior to the O—O bond cleavage.

Thus, these results show that two different electrophilic oxidants, *viz.*, peroxide and ferryl, can hydroxylate alkanes in heme model systems according to the similar assumption[40] for P450. Experiments with chemical models have also shown that the transformation of the peroxide intermediate into ferryl in non-heme systems requires two labile coordination sites at each iron atom in accord with the MMO structure.

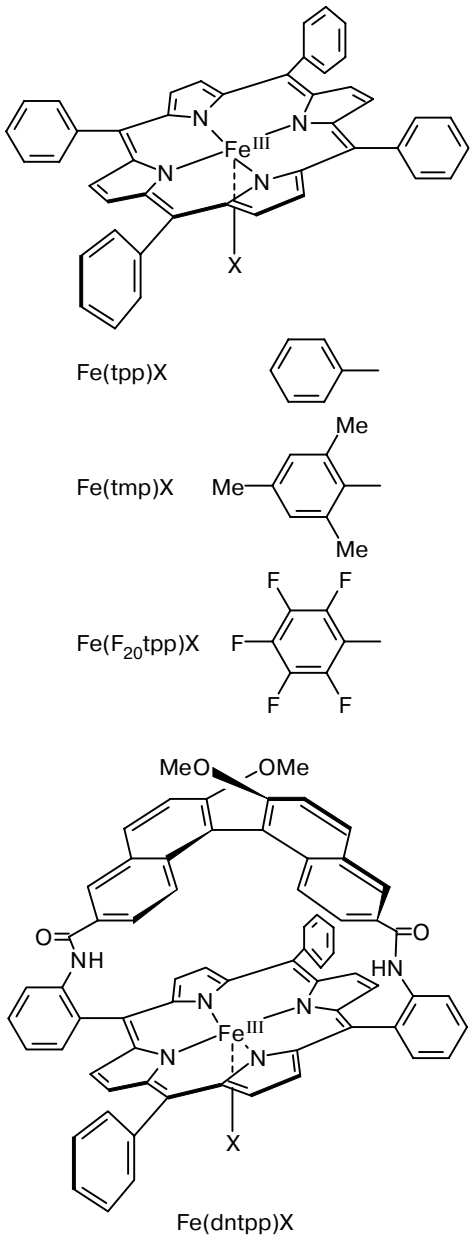
2.4. Oxo intermediates and their involvement in alkane oxidation

Oxo intermediates of the ferryl (Fe^{IV}=O) or perferryl (Fe^{V}=O) types, mononuclear or binuclear, in a heme or non-heme environment, were often assumed as key intermediates in monooxygenases and their models. Reliable evidence for their real participation is presently available.

Peroxidase Compound I, $P^{+\cdot}Fe^{IV}$=O(Im), was isolated and well characterized.[59] Spectral[60] and structural[13] proofs for the formation and key role of the ferryl intermediate of P450, $P^{+\cdot}Fe^{IV}$=O(RS^{-}), in alkane hydroxylation were obtained. The DFT method was used to study the nature of the Fe—S bond and the role of the thiolate ligand in the ferryl intermediate of P450.[61] The calculations gave the geometrical parameters consistent with the X-ray structural data[13] and confirmed the doublet ground state of this intermediate in agreement with the ESR data.[62] The Fe—S bond has a low dissociation energy (6—7 kcal mol^{-1}) and is rather flexible due to the internal charge transfer from the thiolate to the porphyrin ring, and the elongation of the bond is accompanied by a change in the spin state of the complex.

The six-coordinate ferryl complexes $P^{+\cdot}Fe^{IV}$=O(X) (X is the substituent in the *trans*-position to the oxygen atom) were obtained at low temperatures. Their structures were established by various spectral methods, including ESR, ^{1}H NMR, and resonance Raman, Mössbauer, and X-ray absorption spectroscopy.[63,64] The strong *trans*-effect of the O atom on the Fe—X bond length was observed. Spectroscopic evidence for the formation of the $P^{+\cdot}Fe^{IV}$=O(X) intermediate in model systems at low temperatures was obtained,[11,63] this effected regio- and stereospecific alkane hydroxylation even at −40 °C.[11] Based on the temperature dependence of the kinetic isotope effect for the reaction of $P^{+}Fe^{IV}$=O(X) with alkanes, the contribution of proton tunneling to alkane hydroxylation is assumed when P = tmp[65] (Scheme 8). However, no tunneling was found for electron-deficient porphyrins, such as F_{20}tpp [66] (Scheme 8). In the latter case, it is possible to generate $P^{+\cdot}Fe^{IV}$=O(X) using H_2O_2 in the presence of water.[67] The reactivity of the ferryl intermediate, $P^{+\cdot}Fe^{IV}$=O(X), depends strongly on the electronic nature of the axial ligand X which is in the *trans*-position to the O atom.[12,58] The activities of complexes of the PFe^{IV}=O type are much lower than, and differs from, that of PFe^{V}=O[68]: the former can oxidize only very weak C—H bonds and react with alkenes non-stereospecifically.

Scheme 8



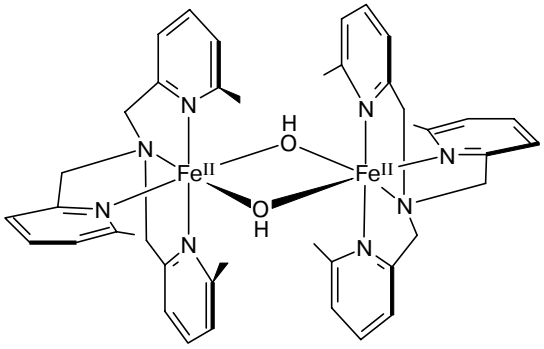
A mononuclear non-heme Fe^{IV}=O complex was obtained in the reaction of ozone with the cyclame iron complex at −80 °C and characterized in a solution by Mössbauer spectroscopy.[69] The involvement of the Fe^{V}=O intermediate with the non-heme environment in the O atom transfer to the C—H bond was proved for the system with the tetradentate ligand bpmen (see Scheme 7), which effected hydroxylation of cyclohexane by hydrogen peroxide in the presence of $H_2{}^{18}O$ [70] (see also Ref. 71). The inclusion of a substantial amount of ^{18}O into the alcohol that formed is related to the well-known exchange between Fe^{V}=O and $H_2{}^{18}O$, whereas its precursor $Fe^{III}OOH$ does not undergo this exchange.

As was indicated above, the ferryl intermediate of MMO was isolated, preliminary data on its structure were obtained, and its involvement in the hydroxylation of alkanes, including methane, was proved. X-ray absorption (EXAFS) and Mössbauer spectroscopic data indicate that intermediate **Q** is a strongly antiferromagnetically coupled Fe^{IV} dimer with an unusually short Fe—Fe distance and short and long Fe—O bonds (for its possible structures see Scheme 5). Theoretical calculations indicate a high probability of structure $\mathbf{Q_a}$.

The recently synthesized oxo-bridged binuclear complexes of high-valence iron $[Fe_2(O)_2(L)_2](ClO_4)_3$ (where L = tpa or its alkyl derivatives) reproduce the assumed bis-μ-oxo-bridged structure of intermediate **Q** and some reactions of monooxygenases.[28] X-ray analysis of the structure of one of these complexes, *viz.*, $[Fe_2(\mu\text{-}O)_2(5\text{-}Et_3tpa)_2](ClO_4)_3$, gives the geometrical parameters of the $Fe^{IV}(\mu\text{-}O)_2Fe^{III}$ core.[72] It has been shown[73] that the $[Fe^{II}_2(\mu\text{-}OH)_2(6\text{-}Me_3tpa)_2](ClO_4)_2$ complex (Scheme 9, *a*) adds O_2 at −40 °C to form bridged peroxide, which is slowly transformed at −30 °C into the $Fe^{IV}(\mu\text{-}O)_2Fe^{III}$ complex, probably, through the $Fe^{IV}(\mu\text{-}O)_2Fe^{IV}$ intermediate (Scheme 10, *a*). Likewise $Fe^{II}_2(\mu\text{-}O_2CAr)_4(4\text{-}Bu^tPy)_2$, where Ar = 2,6-$Ph_2$-4-Me-$C_6H_2$ (Scheme 9, *b*), similarly forms the $Fe^{IV}(\mu\text{-}O)_2Fe^{III}$ complex at −78 °C[74] (Scheme 10, *b*). The complexes with the $Fe^{IV}(\mu\text{-}O)_2Fe^{III}$ core can oxidize only weak C—H bonds,[75] which is not unexpected. Presumably, the postulated active oxidant of MMO, $Fe^{IV}(\mu\text{-}O)_2Fe^{IV}$, must be more reactive because this can perform transfer of the O atom with the insertion into the C—H bond (two-electron process). Calculations show that this process is thermodynamically more favorable than the one-electron abstraction of the H atom. In

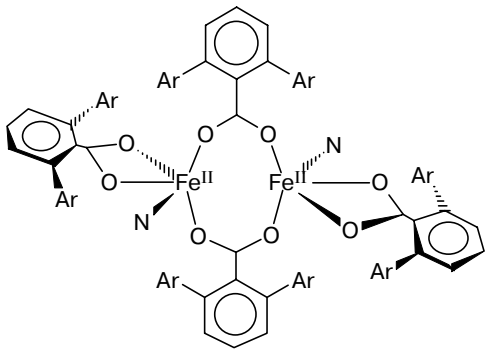
Scheme 9

a



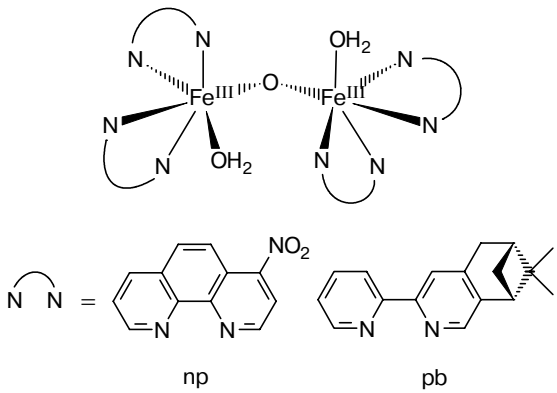
$[Fe_2(OH)_2(Me_3tpa)_2](ClO_4)_2$

b



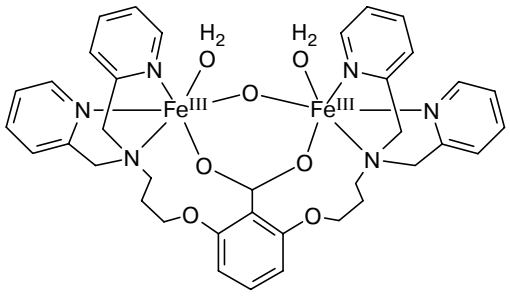
$[Fe_2(Ar'CO_2)_4(Py)_2]$

c



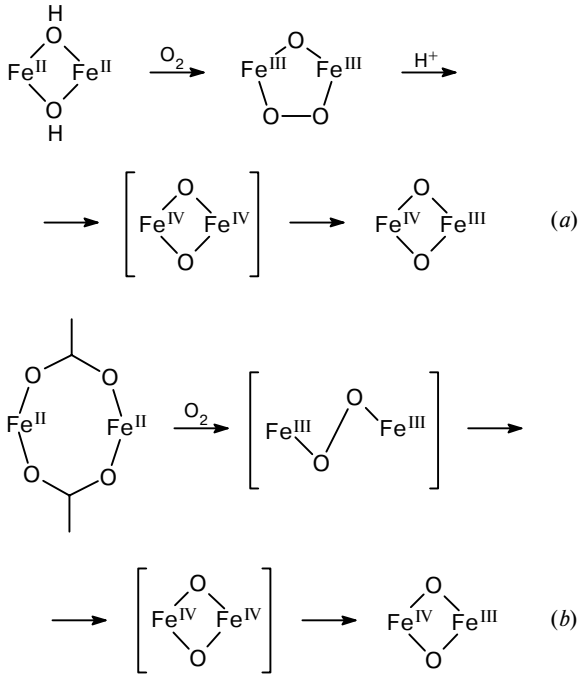
np pb

d



$[Fe_2O(L)(H_2O)_2](ClO_4)_2$

Scheme 10

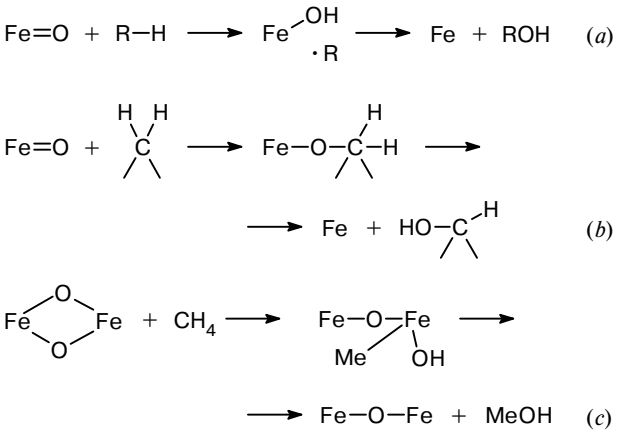


fact, the reaction of the $Fe^{IV}(\mu\text{-}O)_2Fe^{III}$ complex with ethylbenzene is 3 000 000-fold slower than the reaction of intermediate Q with methane: the second-order rate constants are equal to $5 \cdot 10^{-6}$ and 16 $mmol^{-1}\ s^{-1}$, respectively. On the other hand, it cannot be excluded that the open ferryl form of the $Fe^{IV}(\mu\text{-}O)_2Fe^{IV}$ intermediate is active.[29] It turned out[76] that the complex with the $Fe^{III}(\mu\text{-}O)_2Fe^{III}$ core, being oxidized by a strong one-electron acceptor, Ce^{IV}, affords a terminal ferryl complex $Fe^{III}—O—Fe^{IV}=O$, probably, *via* a cyclic intermediate $Fe^{IV}(\mu\text{-}O)_2Fe^{III}$. Similar isomerization is assumed for intermediate **Q** on the basis of quantum-chemical calculations.[30] This is the first example of a binuclear ferryl complex in a non-heme environment.

General features of the structures and reactivities of the ferryl intermediates are clear, while the mechanisms of their reactions with alkanes is disputable.[77,78] Molecular rearrangements which occur presumably *via* free radicals suggested the oxygen rebound mechanism[79] (Scheme 11, *a*). According to this mechanism, the abstraction of the hydrogen atom by the ferryl species to form the alkyl radical is accompanied by fast capture of this radical by the Fe—OH species. However, this mechanism has recently been criticized in the light of new experimental results.[41,80] The use of specially designed substrates (hypersensitive radical probes) which allow the estimation of the lifetime of short-lived radicals and the intermediate formation of carbocations allowed the authors[41,81] to conclude that free radicals are not formed at all in hydroxylation, which occurs as the asynchronous O insertion into the C—H bond with the inclusion of the radical components in the transition state and cationic intermediates. Unfortunately, experimental data for both P450 and MMO do not allow us to choose unambiguously one of the mechanisms. For example, oxidation of a chiral ethane derivative[82,83] affords up to 30% of the product with the inversion of the configuration, which is usually interpreted as the indication to the radical intermediate formation. On the other hand, the hydroxylation of the methyl group of methylcubane without rearrangement of the molecule and without the attack at the C—H bonds in cubane proves the absence of radical intermediates.[84]

The contradictory experimental data could be rationalized in the framework of another mechanism as an alternative to the asynchronous concerted mechanism. This mechanism assumes that the formation of a transient complex, in which the strongly distorted alkane molecule with five-coordinate carbon is bound to the O atom of the ferryl species, precedes the insertion into the C—H bond (Scheme 11, *b*).[80] The possibility of the rearrangement of this intermediate with the formation of the insertion product allows quantitative explanation of many experimental data.[85]

Scheme 11



However, recent studies of ω-hydroxylase by the method of substrate probes[89] showed the involvement of free radicals with the lifetime of an order of nanosecond into the hydroxylation process and provided convincing evidence for the oxygen rebound mechanism.[89] No evidence of the involvement of cationic intermediates into the process was found. The doubtless formation of radicals in this process is compatible with high degree of retention of configuration (25—64%) of the terminal asymmetrical carbon atom in the case of the isotopically substituted methyl group (DTHC).[90] Presumably,[79] the degree of the radical rearrangement should depend critically on the tightness of the radical cage and the combination of steric effects manifested by a particular radical inside the cage. The low degree of rearrangement reflects the easiness of passage from the transition state of H elimination to the transition state of hydroxylation.

It has recently been found[91] for the series of arylmethanes that the kinetic isotope effects in hydroxylation processes involving P450 and the abstraction of the H atom by the *tert*-butoxyl radical are virtually the same, which revived the oxygen rebound mechanism. This mechanism was investigated using the DFT method and the results obtained seem to confirm it provided the inclusion of two ferryl species with the low-spin (doublet) and high-spin (quartet) ground states is taken into account.[92] In the stage of C—H bond extension, the reaction coordinate is virtually the same for both states and coincides with the radical-induced abstraction of H, whereas in the next stage the radical that formed has a substantial barrier to recombination in the high-spin state and in the low-spin state the process occurs without a barrier, *i.e.*, in fact, as an insertion. Calculations explained the results obtained using substrate probes, in particular, the unreally short lifetime of free radicals, and showed that the ratio of the high- to low-spin reaction profiles depends on both the environment in the active center of P450 and the substrate. In the case of strong C—H bonds (in Me groups), the low-spin route is more favorable (*i.e.*, insertion, because a high barrier stands in the high-spin way), whereas weakened benzylic bonds favor decreasing the barriers in both ways, resulting in radical formation.

The early theoretical calculations for MMO using the rather simplified models (see above) supported the insertion mechanism, whereas the later DFT calculations using multiatomic models (40—100 atoms) indicate the initial abstraction of the H atom by the $Fe^{IV}—O—Fe^{III}—O^{\cdot}$ species to form an alkyl radical.[30] Ionization of this radical before alcohol formation is highly probable for all alkanes except for methane. This mechanism containing a stage of a radical cation transformation allows combining of the initial abstraction of $H^{\cdot}$ with the high retention of the configuration in hydroxylation. It was mentioned[30] that no spin effects, unlike P450, are substantial for MMO.

3. Chemical analogs of monooxygenases: regio-, stereo-, and enantioselective oxidation of alkanes to alcohols

Synthetic metal porphyrin complexes had a strong impact on the development of concepts on the active ferryl intermediate of P450 and routes of its formation from the $Fe^{II}O_2$ complex, on the influence of electronic effects on the O—O bond cleavage, and on the role of the porphyrin and thiolate ligands in P450 functioning. In the case of MMO, the problem of choosing model complexes turned to be much more complicated because the iron complexes with simple (mono- and bidentate) ligands are, as a rule, kinetically unstable in solutions. The solution can be found by using polydentate or macrocyclic ligands[93—96] or by the introduction of bulky groups into ligands protecting coordination sites on the metal. Nevertheless, the nature of the peroxide (**P**) and, in part, ferryl (**Q**) intermediates of MMO was elucidated using relatively simple non-heme complexes, as well as the stability of ferryl in the non-heme environment and its participation in stereoselective alkane oxidation were demonstrated.

On the other hand, chemical modeling of monooxygenases, along with the necessity of a deeper insight into the essence of enzymatic catalysis, is stimulated by the fact that the directed monooxygenation of definite C—H bonds in alkanes and other compounds is a challenging problem of organic chemistry.[97—99] Monooxygenases discussed in this review can efficiently catalyze the hydroxylation of rather inert compounds (such as alkanes) under mild conditions with high selectivity. It is even more important that these enzymes perform the regio- and stereoselective insertion of the O atom into non-activated C—H bonds of various compounds in one stage. An exciting example for comparison of the traditional chemical and biocatalytic approaches is the directed enzymatic hydroxylation of progesterone at the 11β position (despite the presence in this molecule of several other, equally and even more reactive C—H bonds), which represents a simple synthesis of cortisone replacing 31 stages of the chemical synthesis from cholic acid.[100] Since these reactions are significant for both synthetic chemistry and chemical industry, biomimetic oxidation involving synthetic complexes became of great interest in recent years.[97,100]

Iron tetraphenylporphyrin complexes Fe(tpp)Cl and Fe(tmp)Cl were the first simple models, which allowed the O atom transfer to double bonds of alkenes and C—H bonds of alkanes. They catalyzed the hydroxylation of alkanes and epoxidation of alkenes with iodosobenzene (PhIO).[101,102] Later these models were substantially improved by the introduction of electron-withdrawing substituents into the phenyl groups of the porphyrin and then by the complete halogenation of the porphyrin ring (Scheme 8). This decreased the oxidative degradation of the ligand and increased the reactivity of

the intermediate (Table 1). Very efficient catalysts were synthesized based on such electron-deficient porphyrins, and they provided high yields of products at high rates of the oxidation of hydrocarbons, including inert *n*-alkanes.[103,104] The models using such oxygen donors as H_2O_2, PhIO, NaOCl, and others have gained the largest development, whereas the creation of the models employing O_2 as the oxidant required higher degree of organization of the catalyst and was hampered by the difficulty of elimination of the competition between the substrate and the reducing agent for the active oxygen. The perfection of the models based on tetraphenylporphyrin complexes included the protection of active O by the introduction of steric hindrances into its environment and the creation of conditions for the coordination of the axial ligand only at one side of the heme to preserve the second axial site for catalysis. The efficiency and stability of the catalyst increase substantially when bulky substituents are introduced into the *ortho*-positions of the phenyl rings of the tetraphenylporphyrin and electronegative substituents into the porphyrin ligand. Manganese and ruthenium porphyrinates often compared favorably in model systems with iron porphyrinates. Some examples of the biomimetic oxidation of alkanes or alkyl fragments of molecules are presented in Table 1. It is seen that biomimetic oxidation has many remarkable features of biocatalytic oxidation. The yields of the main products are higher than 80%, and in most cases they reach 90—100%. The oxidation rate can be very high. For example, the rate of hydroxylation of a tertiary CH bond in adamantane (Table 1, entry 4) at 65 °C reaches 1000 turnovers of the catalyst per min. High regio- and stereoselectivity is observed. The configuration of the chiral carbon in *cis*- or *trans*-1,2-dimethylcyclohexane and (*R*)-(1-deuterioethyl)benzene is retained upon hydroxylation (Table 1, entries 3, 5, 9 and 10 and entry 8). The hydroxylation of the prochiral methylene group in ethylbenzene (entries 8 and 10) affords the chiral products with high or moderate enantioselectivity. In most cases, the efficiency of the employment of the oxidant is above 60%. The use of H_2O_2 as a cheap and environmentally clean oxidant for the biomimetic oxidation of hydrocarbons seems especially attractive. It has been shown in recent years that the biomimetic oxidation of alkanes by hydrogen peroxide can be achieved with satisfactory efficiency using the non-heme complexes (entries 9 and 10), and in the case of models of P450, the electron-deficient porphyrins were used (entry 3).[66,67,103]

Table 1. Biomimetic alkane oxidation with the formation of the corresponding alcohols and ketones

Entry	Starting alkane	Products	Catalyst[a]	Oxidant	Solvent	*Y*[b] (%)	*S*[c] (%)	*Ss*[d] (%)	Refs.
1	Cyclohexane (C_6H_{12})	...-ol + ...-one 10 : 1	Fe(tpp)(Cl)	PhIO	Benzene	26	91	—	102
2	C_6H_{12}	...-ol	Fe(F_{20}tpp)(Cl)	PhIO	CH_2Cl_2	67	100	—	104
3	C_6H_{12}	...-ol + ...-one 30 : 1	Fe(F_{20}tpp)(NO_3)	H_2O_2	MeCN+ +CH_2Cl_2 (1 : 1)	31	97	100[e]	67
4	Adamantane	...-1-ol + ...-1,3-diol 10 : 1	Ru^{II}(F_{20}tpp)(CO)	2,6-Cl_2PyO	CH_2Cl_2	97	91	—	112
5	*cis*-1,2-$Me_2C_6H_{12}$	*cis*-...-1-ol + + *sec*-...-ol 74 : 19	Fe(F_{20}tpp)(CF_3SO_3)	*m*-ClC_6H_4— —C(O)OOH	MeCN+ +CH_2Cl_2 (1 : 1)	93	80	100	66
6	Norbornane	*exo*- + *endo*-...-ol 55 : 5	Fe(F_{20}tpp)(CF_3SO_3)	*m*-ClC_6H_4— —C(O)OOH	MeCN+ +CH_2Cl (1 : 1)	60	100	91	66
7	$Bu^tC_6H_{12}$	4-*trans*- + *cis*-...-ol 4 : 1	Fe(tmp)(Cl)	PhIO	CH_2Cl_2	—	100	80	104
8	Ethylbenzene	(*R*)- +(*S*)-1-Ph-...-ol 85 : 15	Fe(bntpp)(Cl)	PhIO	CH_2Cl_2	40	70	100[f]	113
9	C_6H_{12}	...-ol + ...-one 8 : 1	Fe(bpmen)$(MeCN)_2(ClO_4)_2$	H_2O_2	MeCN	70	90	100[e]	114
10	C_6H_{12}	...-ol + ...-one 3 : 1	$Fe_2O(pb)_4(H_2O)_2(ClO_4)_4$	H_2O_2	MeCN	30	75	100[e,g]	115

[a] See Schemes 7—9 for structures of complexes used as catalysts.
[b] *Y* is the yield calculated per oxidant (%).
[c] *S* is selectivity (%).
[d] *Ss* is stereospecificity(%).
[e] Retention of the configuration upon the oxidation of the tertiary CH bond in *cis*- and *trans*-1,2-dimethylcyclohexanes in this system.
[f] Retention of the configuration upon oxidation of *R*-PhCHDMe, *ee* 70%.
[g] This system also manifests a moderate enantioselectivity for the oxidation of ethylbenzene (*ee* 7%) and dimethylindane (*ee* 15%).

The modification of the nearest environment of the O atom bound to the metal, for example, by the introduction of bulky or chiral groups into the *ortho*-positions of the phenyl rings of tpp, allows one to coltrol the regio- and enantioselectivity of the oxidation. The catalytic asymmetrical monooxygenation of alkanes, alkenes, and alkyl sulfides was achieved with the Fe and Mn complexes of binaphthyltetraphenylporpyrin (Scheme 8; Table 1, entry 8). The introduction of bulky substituents into the porphyrin directs the regioselectivity of *n*-alkane oxidation toward an increase in the oxidation of the terminal (ω) methyl group and/or adjacent methylene (ω-1) group (shape-selectivity).[11,105] For example, when the very sterically hindered tetraphenylporphyrin with eight phenyl substituents in the *o*-positions of the phenyl rings of tpp (Scheme 8) was used, the selectivity of *n*-heptanol formation with respect to other isomeric alcohols can be increased from trace amounts (for nonsubstituted tpp) to 26%.[106] In other approach, steric hindrances in porphyrin were created by using interactions of the "host—guest" type between the porphyrin with four *n*-alkyl substituents and cyclodextrins with hydrophobic cavities, which can incorporate these alkyl "tails." For the oxidation of *n*-hexane in this biomimetic microheterogeneous system the selectivity of *n*-hexanol formation reaches 30%.[107] The fact of the formation of primary alcohols from *n*-alkanes makes these systems close to ω-hydroxylase.

The selective formation of alcohols upon oxidation of alkanes or of epoxides upon oxidation of alkenes, stereo-, enantio-, and shape-selectivity can serve as tests for proving the O transfer in model systems.[11,101]

Very perfect models of cytochrome P450 were developed[108] on going from simple sterically hindered metal porphyrinates to systems with hydrophobic cavities constructed by either covalent bonding of molecules with cavities (cyclodextrins, cyclophanes) or self-assembling to organized molecular ensembles using noncovalent interactions. These models contain all the components of natural catalysts, use molecular oxygen as an oxidant, and operate with rates and selectivities close to those attainable with enzymes.[108] The majority of such models are designed for controlled alkene epoxidation, which is an unambiguously simpler problem than controlled alkane hydroxylation.

Despite great efforts, the efficient oxidation of methane using the well characterized model complexes[109,110] has not been performed yet, although the biomimetic oxidation of cyclohexane with mononuclear non-heme complexes has recently been carried out (Scheme 7; Table 1, entries 9 and 10). The highly selective oxidation of methane to methanol by N_2O on zeolite FeZSM-5 is very encouraging. This oxidation has some features of monooxygenase oxidation, although the nature of iron-containing active centers and intermediates, as well as the oxidation mechanism, are insufficiently studied.[111]

Thus, modeling of non-heme monooxygenases capable of alkane oxidation, in fact, is in the very beginning, whereas the biomimetic models of P450 have reached high perfection, essentially approaching biological catalysts in structural and functional characteristics.

4. Conclusion

The insertion of the O atom into the C—H bond is one of the remarkable reactions existing in Nature. Recent studies showed that the best studied monooxygenases (P450, MMO, ω-hydroxylase) have many common features in the mechanisms of O_2 activation and alkane oxidation. The active oxidant of all these monoxygenases contains the high-valence iron with the terminal or bridging oxo ligands, and it is preceded by the peroxide intermediate formed by the reduction of the dioxygen complex. Although the involvement of the hydroperoxide intermediate in the reaction with alkanes is also assumed in the case of P450, direct experiments are still lacking.

The biomimetic oxidation of alkanes by chemical models of P450 compares favorably in the efficiency and selectivity with that catalyzed by enzymes. However, much effort should be focused on the creation of model systems which employ dioxygen as the terminal oxidant. Efficient models of MMO have not been created so far. Although alkane oxidation by hydrogen peroxide catalyzed by biomimetic iron complexes is a remarkable achievement, great skill of synthetic chemists will be required to create an adequate model of MMO capable of oxidation of methane. Perhaps, the progress in this area is hampered by insufficient knowledge of the mechanism of reactions of MMO. Advances in the correct quantum-chemical calculations of polyatomic systems containing transition metals allows us to hope that realistic calculation methods will in future play an increasing role for understanding of the mechanism of reactions of metal enzymes, including monooxygenases.

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