Five-coordinate carbon hydroxylation mechanism

A.F. Shestakov, A.E. Shilov *

Institute of Chemical Physics in Chernogolovka, Russian Academy of Sciences, Chernogolovka, Moscow Region, 142432, Russia

Abstract

Oxygen rebound mechanism for hydrocarbon hydroxylation by high-valent metal complexes is critically analyzed and is shown to be contradictory in certain aspects. The synchronous insertion of O atom mechanism is found to be significantly less contradictory (at least for the most interesting cases of strong C–H bonds, for example in methane) if it is supplemented by the stage of formation of the five-coordinate carbon intermediate complex of a hydrocarbon molecule via oxygen atom of an active center.

Keywords: Mechanism; Hydrocarbons; Metal complexes; Hydroxylation

High-valent oxygen containing metal complexes are able to transfer oxygen atom to an acceptor molecule in different reactions: olefin epoxidation, CO oxidation, N-oxides formation from amines, hydroxylation of aromatic and aliphatic hydrocarbons [1,2]. The particular interest to these reactions was arisen when it was realized that they are involved in the key stage of the enzymatic oxidation by monooxygenases. Hydroxylation of the aromatic and aliphatic C–H bond and epoxidation of olefins by cytochrome P-450 apparently includes formation of an active species P^+ $Fe^{IV}O$, where P is porphyrin ligand [3,4]. Methanemonooxygenase (MMO), hydroxylating methane, presumably also includes oxygen atom in iron coordination sphere in dinuclear complex in mononuclear $Fe^{IV}O$ fragment [5] or a bridging oxygen atom in a dinuclear $Fe^{IV} < {O \atop O} > Fe^{IV}$ fragment [6].

For a number of substrates they form intermediate complexes which are known or may be easily suggested, e.g. in the case of the olefin epoxidation and hydroxylation of aromatic compounds, the reaction of oxygen transfer includes the formation of an intermediate complex via bonding of O atom to carbon atom of an unsaturated molecule. In the case of the hydroxylation of alkanes saturated character of C–H bond seems to preclude formation of analogous intermediate complex. Usually two alternative mechanisms for enzymatic oxidation of C–H bonds and their chemical analogues are considered: (1) synchronous insertion of O atom bound to metal into C–H bond and (2) so called 'oxygen rebound mechanism' (ORM) involving H atom abstraction from a hydrocarbon followed by recombination of a radical formed with OH

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* Corresponding author.

group on the metal [7]. Recently it is the latter mechanism that obtained general support although thermodynamically the former mechanism is more favourable. The following evidences for ORM mechanism are usually considered:

1. High isotope effect (k_H/k_D achieves 10–12) [8]. This is explained by linear transition state Fe–O...H–R, while the O atom insertion into C–H bond is expected to correspond to a smaller isotope effect.
2. Isomerisation observed in the molecules of products. It is explained by the isomerisation in free radical intermediately formed. When the time of the radical isomerisation is known, from the ratio of isomerised to non-isomerised products the rate constant of the 'oxygen rebound' step can be estimated (the 'radical clock' method) [9].
3. The use of radical traps. For example, the presence of radical traps during methane oxidation by MMO shows the involvement of methyl radicals [10].

We shall show that in spite of apparent persuasiveness of these arguments, their consistent consideration leads to certain contradictions. We believe that the synchronous insertion of O atom mechanism is significantly less contradictory (at least for the most interesting cases of strong C–H bonds, for example in methane) if it is supplemented by the stage of *formation of the five-coordinate carbon intermediate complex of a hydrocarbon molecule via oxygen atom of an active center*.

Let us consider arguments proposed in favour of the oxygen rebound mechanism more thoroughly.

1. High isotope effect. Actually isotope effect often exceeds the maximum value, which is evaluated from difference between zero energies of the initial and transition state ($k_H/k_D)_{max} \sim 8$ and it points to an electron tunneling mechanism. Indeed the participation of the H atom tunneling is shown for rate determining step in cytochrome P-450 models on the base of analysis of the temperature dependence of the isotope

$$Ph \triangle CH_3 \longrightarrow Ph \triangle CH_2OH + C_6H_4OH \triangle CH_3$$
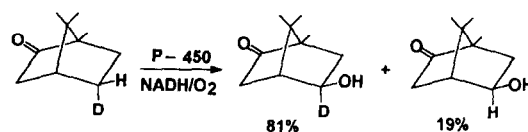
Scheme 1.
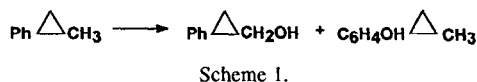
effect [11]. If the tunneling is proven for certain cases, generally speaking, it is impossible to reject its contribution in those cases, in which kinetic isotope effect is close to 8 or even smaller. Therefore, high values of kinetic isotope effect may be merely an indication of proton tunneling which could be due to a reaction mechanism not necessarily involving linear transition state.

2. The isomerisation in reaction products is not always observed. E.g. it is shown in [12], that in enzymatic oxidation of 1-methyl-2-phenylcyclopropane, catalyzed by MMO, the cyclic molecules containing hydroxylated methyl and phenyl groups are the only products and no isomerisation takes place (Scheme 1). The radical life-time before the cycle opening is known to be very short in this case and to explain the absence of the isomerisation products the rate constant for the 'oxygen rebound' step must be higher than 4×10^{13} sec^{-1}, i.e. the time of this transformation must be less than the time of one vibration. Recent results of isomerisation of certain cyclopropane derivatives in the process of their hydroxylation have shown unexpectedly short times of oxygen rebound steps and require some new postulates to reconcile the results with the oxygen rebound mechanism [9].

On the other hand the fact of an isomerisation, if it is observed, is not necessarily connected with intermediate radical formation, but may be caused by another intermediate also capable of isomerisation. It may be noted that in the case of the enzymatic or pure chemical olefin epoxidation and aromatic compounds hydroxylation there is the parallel isomerisation with H atom shift (in the first case the aldehydes are often formed together with epoxides, in the second one so called NIH shift takes place: D atom transfer to neighbouring position of aromatic ring). Here isomer formation shows
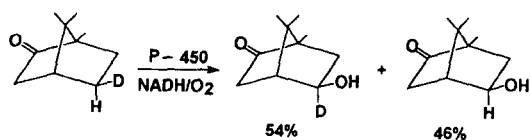
Scheme 2.

Scheme 3.

the existence of active intermediate complexes, but not free radicals.

In some enzymatic hydroxylations of an aliphatic C–H bond the isomerisation observed does not correspond to radical formation. In selective hydroxylation of the camphor by cytochrome P-450 5-exo-hydroxocamphor is selectively formed. In this case in exo D-substituted camphor D atom partially goes to endo-position ('D-shift') (Scheme 2).

In 5-D-endo-substituted camphor some D shift also proceeds while only exo-hydroxylation takes place [13] (Scheme 3).

For oxygen rebound mechanism no isomerisation would be possible since no rotation of the molecule as a whole is allowed. The authors of [13] suppose that the camphor reacts with some other radical during hydrogen or deuterium atom abstraction and after that interacts with Fe–porphyrin complex in stereoselective reaction. At present the structure of the camphor cytochrome P-450 active center is known and the assumption about the additional radical finds no confirmation. It is more natural to suppose that in an non-radical intermediate formed a rearrangement, which is equivalent to transposition

of the endo- and exo-hydrogen atoms, with some (small) barrier is possible. From this point of view the considerable epimerization observed in exo,exo,exo,exo-2,3,5,6-tetradeuteronorbornane oxidation [14] by cytochrome P-450 and in model systems [15] (Scheme 4) may be due to the same cause.

An analogous non-radical intermediate may be suggested for ethane $^1H^2H^3HCCH_3$ isomerisation during its hydroxylation by MMO where the formation of intermediate free ethyl radicals is proposed [16] (Scheme 5).

In some cases (for example allyl rearrangement) the compounds with weak C–H bond were used, where free radicals may actually form [17]. If to suppose that two reactions of intermediate complex compete: synchronous oxygen insertion into C–H bond and hydrogen abstraction with free radical formation, then the decreased C–H bond energy will increase the part of the radical transformation. The nature of metal bound to oxygen atom can essentially influence the ratio of these reactions. For example, the allyl rearrangement was not observed at oxidation of 3,3,6,6-d_4-cyclohexene by the high-valent $Ru^{IV}=O$ oxocomplex and the value
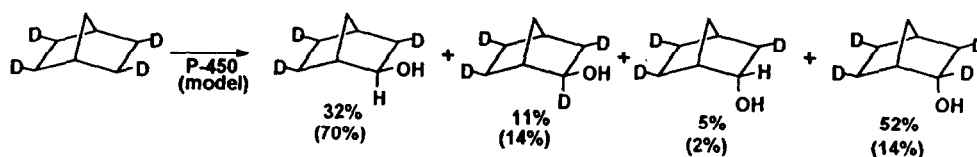

Scheme 4.
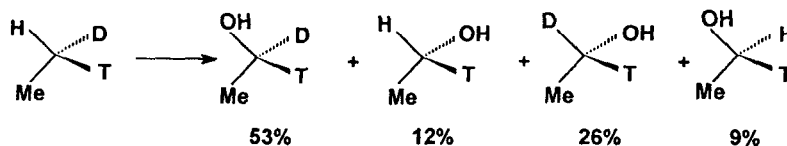
Scheme 5.

of kinetic isotope effect was equal to $k_H/k_D =$ 18 at 25°C [18].3. Radical traps can indicate both the parallel (not quantitative) formation of free radicals and the reaction of intermediate complex whose alkyl group can acquire sufficient mobility (because of the weakening of bond energy) for reaction with traps.

There are some doubts about thermodynamic possibility of radicals formation in the alkane reactions with FeO fragments of the active center especially in the cases of strong C–H bonds. For C–H bond radical cleavage high C–H bond dissociation energy of (80–105 kcal/mol) must be compensated. We can judge the value of ferryl complex redox potential on the basis of data [19] on electrochemical oxidation–reduction of oxo-tetrakis-5,10,15,20(N-methyl-4-pyridyl) porphyrin iron(IV) complex in water at pH < 10.5 according to the equation

$$TMPFe^{III}OH \rightarrow TMPFe^{IV}O + H^+$$
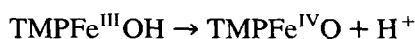
The potential of half-wave at pH = 8 was found to be equal to 0.65 V relative to chlorine–silver electrode and has a shift of +58 mV at a pH increase of 1. Therefore the ferryl complex standard potential (relative to hydrogen electrode) is equal to ~ 1 V at pH ~ 6 and it is unlikely that redox potentials of active intermediate complexes in cytochrome P-450 differ considerably from this value.Meanwhile the redox potentials of formation of radicals from hydrocarbons:

$$RH - e \rightarrow R + (H)^+_{aq}$$
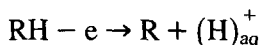
are large particularly for primary and secondary radicals. According to our estimate [20] these potentials for $HCH_{3-n}(CH_3)_n$ ($n = 0, 1, 2, 3$) and HCH_2Ph are equal to 2.25, 2.00, 1.84, 1.60 and 1.44 V respectively. Thus only in the case of less stable tertiary and activated C–H bonds could noticeable rates for radical mechanism be expected. Two-electron hydroxylation of alkanes is thermodynamically much more favorable and the absence of radicals would be much safer for organisms. Moreover, the dinuclear structure of MMO [21] is of course favorable for a two-electron mechanism.

We treat the hydroxylation mechanism problem taking into account that at present there are a number of direct and indirect arguments in favour of the formation of complexes of hydrocarbons both with electron-rich metal centers [22–24] and various electrophilic particles [25,26]. The property of hydrocarbons to form a complex is due to the possibility of coordination numbers to increase for C and H atoms to 5 and to 2 respectively [27]. This usually takes place in dimeric aluminium alkyls and in complexes with an agostic C–H bond. The 7-norbornyl cation with 5-coordinated C atom [28] is known and has been structurally characterized. There is one example [29] of 5-coordinate carbon species with 2 sulfur atoms bound to carbon atom. The structure of complexes of methane with metal centers is investigated theoretically [30–32] and it is found that energy of their formation achieves 12–18 kcal/mol.

Apparently a protonated methane is the most studied system with five-coordinate carbon. The theoretical study of its structure on the base of high level non-empirical calculations shows that the ground state of CH_5^+ is with symmetry C_s and it differs only by ~ 1 kcal/mol in energy from exited state with C_{4v} symmetry. The C_{2v} symmetry state is also disposed closely (the energy difference is 0.9 kcal/mol). D_{3h} isomer of CH_5^+ has the highest energy. There are groups of structurally equivalent C–H bonds in all isomers (due to small value of barrier of H–H rotation with respect to CH_3.
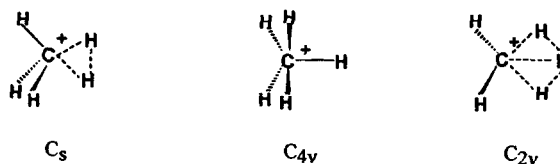
Hydrogen atoms 'travel' freely between many equivalent minima due to easy pseudo rotation in CH_5^+ so the single stable equilibrium structure is absent [33]. There is no doubt that under H^+ action there would be complete hydrogen
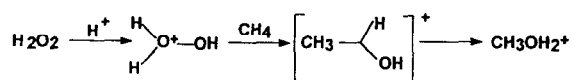
Scheme 6.

scrambling in hydrocarbons leading to isomerisation in chiral molecules without intermediate free radical formation.

Other electrophiles (E) are able to attack alkanes in superacid media via electrophilic addition of E to C–H bond. In particular O atom insertion is observed in protonated hydrogen peroxide reaction with methane to produce methyl alcohol with very high (> 95%) selectivity. Olah [34] proposes the scheme depicted in Scheme 6 for the reaction.

In this case H atoms scrambling is very likely to proceed as well as in CH_5^+ since some structurally equivalent C–H bonds will probably exist in the intermediate similarly to CH_5^+ or the barriers for H atom shift reach equivalent position will be low.

Interaction of NO^+ with methane was found to proceed via the formation of the complex of 5-coordinate carbon [35], (a)


(a)   (b)
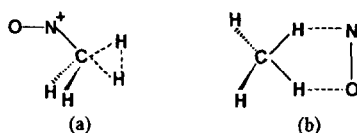
This complex corresponds to the main CH_5^+ structure, though there is a significant barrier of 65 kcal/mol at its formation from the weak complex (b). However the barrier for the straight insertion of NO^+ into the C–H bond is even higher (80 kcal/mol).

Recent theoretical results show [36] that the methane inversion, through a complex of carbene with dihydrogen, requires roughly the same energy as inversion through C–H bond cleavage. The main contribution in distorted methane stabilization under two H atoms closing in, is provided by the donor–acceptor interaction of the hydrogen pseudomolecule σ orbital and

unoccupied methylene orbital just as in well known complexes of molecular hydrogen. At the deformation of methane with new coordination site forming, the highest occupied MO of CH_4 achieves good localization in the region of this site. This orbital is very suitable for donor–acceptor interactions in methane complex. H_2O and CH_4 molecules have proton affinities 7.14 and 5.3 eV respectively [37]. The energy requirement needed for distortion of CH_4 structure (like in the CH_4 fragment of CH_5^+) will be added to methane proton affinity, therefore, we can conclude that distorted methane actually possesses a lone pair. For example angle deformation of CH_4 to flatten the CH_3 fragment requires by our estimate about 17 kcal/mol in harmonic approximation based on experimental force field. Quantum chemical calculation gives a similar estimate [38].

The lowest unoccupied MO of deformed methane has antibinding properties between C atom and H_2 pseudomolecule. As the association of H atoms results in some moving them away from C atom, this orbital is noticeably lower in energy than the usual anbinding C–H orbitals. As a result a distorted methane is not only a good donor but also an acceptor. It is important because of a methane activation by ferryl particle takes place in the presence of water which is a better donor than methane. Had methane been only a donor it would not be able to compete with water in the interaction with the acceptor active center. Therefore the existence of two interaction channels, acceptor–donor and back donation ones, between ferryl particle and distorted methane gives the possibility of its more effective interactions as compared with water due to the mutual compensation of transferred charges.
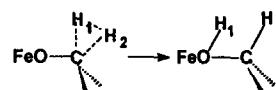
In the case of distortion of highly symmetrical methane molecule the ν_1 vibration (forbidden for exact T_d symmetry) becomes allowed in IR spectra. Indeed for methane, adsorbed on zeolites and on CeO_2 surface this vibration [39,40] was observed. It is interesting to note that on treatment of Fe-containing zeolite ZSM-5
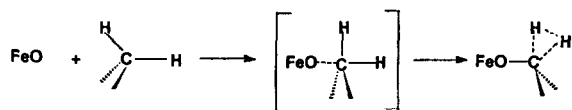
Scheme 7.
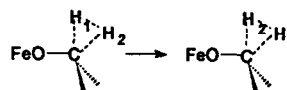
Scheme 9.

Scheme 10.

with N_2O, oxygen atom is transferred to iron, to form an active center at which methane hydroxylation takes place under mild conditions [41].

The analysis of the reaction coordinate for the interaction of ferryl with a hydrocarbon shows that the process is as follows. At the initial stage of the interaction the C_{3v} type deformation of hydrocarbon takes place (Scheme 7) with the subsequent structural relaxation due to bringing two H atoms together and lengthening of the corresponding C–H bonds. Since the methane activation is reached because of soft deformation movements, it is natural to conclude that activation energy of the complex formation will be lower than for the reaction of radical formations with the same energy requirement.

It is easy to see that the coordinate of the complex rearrangement at the beginning is close to the coordinate of the radical formation (Scheme 8).

Therefore in the case of its thermodynamic possibility the parallel formation of both the radical and the final product alcohol is possible from initial complex. It may be suggested that the barrier of H...H fragment rotation with respect to C atom is not large due to noticeable lengthening of $C–H_1$ and $C–H_2$ bonds in LFeO–RH complex, so the D-shift reaction takes place easily (Scheme 9).

The transition of the complex into main form of coordinated alcohol is produced due to O–$C–H_1$ angle decrease (Scheme 10).

In a sense this reaction may be considered as H–H bond cleavage in the field of LFeO=C <
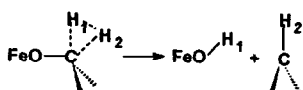
core, and this may cause an increase of ultimate value of the thermodynamic isotope effect. For example in the complex of ethane with proton of classical $C_2H_5–H_2^+$ structure the H–H vibration frequency is $3964 \ cm^{-1}$ [42], which is only 10% less than that of hydrogen molecule (4401 cm^{-1}). In this case apart from displacement of H_1 atom there is also some displacement of H_2 atom. That is why additional possibilities arise for the high value of k_H/k_D kinetic isotope effect due to H atom tunneling through narrow barrier.

There is some indirect evidence that the reaction between ferryl active center and alkane molecule proceeds via addition rather than C–H bond radical cleavage. In particular the ratio of cyclopentane to cyclohexane activity (so called C_5/C_6 factor) in iron porphyrin complex less than unity (reaches 0.3–0.4) [43], which corresponds to initial addition. However we realize that there is still lack of direct experimental evidence of the proposed mechanism. We hope that such evidence will appear in future investigations.

Scheme 8.

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