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FEATURE ARTICLE

‘Oxo-hydroxo tautomerism’ as useful mechanistic tool in oxygenation reactions catalysed by water-soluble metalloporphyrins

Jean Bernadou*† and Bernard Meunier*†

Laboratoire de Chimie de Coordination du CNRS, 205 route de Narbonne, 31077 Toulouse cedex 4, France

High valent metal–oxo species have been evoked as active intermediates in many different oxidation reactions using manganese or iron porphyrin complexes as catalysts and oxygen atom donors (H_2O_2, PhIO, NaOCl, $KHSO_5$, ... *etc*.) or dioxygen associated to a reductant as oxygen atom source. When these metalloporphyrin-catalysed oxidations are performed in water, such metal–oxo species are able to transfer an oxygen atom coming from either the oxygen source or from bulk water. This fact has been explained by the so-called oxo–hydroxo tautomerism, a mechanism involving a rapid shift of two electrons and one proton from a hydroxo ligand (electron-rich ligand formed by deprotonation of an aqua ligand) to the trans oxo species (electron-poor ligand) leading to the transformation of the hydroxo ligand into an electrophilic oxo entity on the opposite side of the initial oxo. This ‘oxo–hydroxo tautomerism’, evidenced by using ^{18}O-labelled water, has been used as mechanistic tool to unambiguously characterize oxygen atom transfer mechanisms mediated by metal–oxo species in opposition to mechanisms related to free radical oxidation reactions.

Introduction

High-valent metal–oxo intermediates play an important role in catalytic processes involving dioxygen activation and O-atom transfer reactions performed by hemoproteins such as cytochromes P-450 and some peroxidases.[1,2] For example, the so-called Compound I of peroxidases (Cpd I), with two oxidizing equivalents above the ferric state, has been characterised in horseradish peroxidase as an iron(IV)–oxo porphyrin π cation radical, and the great reactivity of P-450 is believed to derive from a formal iron(V)–oxo porphyrin species acting as ultimate oxidant.[3–6] Compound II (Cpd II), the second catalytic intermediate of peroxidases, is an iron(IV)–oxo with only one oxidizing equivalent above the resting state of the corresponding native heme–enzyme. There is no Cpd II intermediate in the catalytic cycle of cytochrome P-450.

$Por\text{-}Fe^{III}$
native state of P-450 or peroxidase

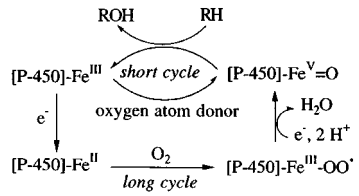
$Por\text{-}Fe^{V}{=}O$ or $(Por^{\bullet+})Fe^{IV}{=}O$ — P-450 active species or Cpd I

$Por\text{-}Fe^{IV}{=}O$ — Cpd II

The recent discovery of oxo–hydroxo tautomerism can contribute to a better characterisation and an improved understanding of chemical reactivities of these high-valent metal–oxo species, not only important for the knowledge of heme-enzymes catalyzing oxidations, but also in the design of efficient biomimetic or bioinspired oxidation catalysts. After a short survey on the characteristics of high-valent metal–oxo complexes, this Feature Article will be focused on the oxo–hydroxo tautomerism.

High-valent metal–oxo species in heme-enzymes and related chemical models

The oxidative reactions mediated by cytochrome P-450 are better described with an iron(V)–oxo as active entity than with any other putative species. Taking in consideration all the different experimental data accumulated for the last three decades on cytochrome P-450, it is reasonable to assume that hydroxylation of alkanes, epoxidation of electron-rich alkenes and formation of *N*-oxides are performed by an electrophilic high-valent iron(V)–oxo rather than by a nucleophilic Fe^{III}–OOH intermediate. The high oxidation state of iron in the perferryl $Fe^{V}{=}O$ species might be reduced by transfering one electron from the sulfur atom of the cysteinato proximal ligand, or from the porphyrin ligand like in peroxidases [ferryl is used for an iron(IV)–oxo species; perferryl is used for an iron(V)–oxo species or an iron(IV)–oxo with a radical cation on the macrocyclic ligand, like in Cpd I of peroxidases].[5b,7] This audacious hypothesis has been supported by establishing in 1975 that a single oxygen atom donor, namely iodosylbenzene PhIO, was a suitable co-factor for a P-450 mediated O-dealkylation reaction.[8] Then, the modeling of peroxide shunt in the catalytic cycle of cytochrome P-450 (short cycle in Scheme 1)



Scheme 1 Catalytic cycle of cytochrome P-450 with the formation of an iron(V)–oxo species (or an iron(IV) radical-cation as in Cpd I of peroxidases) *via* a ‘long catalytic cycle’ with dioxygen, two electrons and two protons or *via* a ‘short cycle’ (peroxide shunt) with oxygen atom donors (PhIO, NaOCl, $KHSO_5$, H_2O_2)

was demonstrated with synthetic metalloporphyrins using PhIO, NaOCl, $KHSO_5$ or H_2O_2.[2,5b,9–12] There is no physical characterisation of the putative iron(V)–oxo for cytochrome P-450 itself because of its very short lifetime, but its orbital diagram based on different calculations has been described by several groups.[13,14] The reactive high-valent iron or manganese–oxo species are usually depicted with a double-bond between the metal and the oxygen atom [complex **A** in Scheme 2, case of an iron(V)–oxo species]. This classical way to represent a metal–oxo bond is convenient to describe the oxidation state of the metal, but one drawback is that the same formalism is used for the non-labile $Ti^{IV}{=}O$ derivative as for the highly reactive $Fe^{V}{=}O$ or $Mn^{V}{=}O$ complex. In fact, the electronic structure of the form **A** with a metal–oxygen double bond is probably higher in energy than the diradical form **B**, an iron(IV)–oxoid species, in a similar way as singlet dioxygen, with a double bond, is higher in energy by 23 kcal mol^{-1} (1 cal = 4.184 J) compared to the triplet ground state, with a single O–O bond and two unpaired electrons (the name ‘oxoid’ underlines the reduction of the bond order between the metal

Form **A** ('singlet state') Form **B** ('triplet state')
d^3 iron(V)–oxo d^4 iron(IV)–oxoid

Scheme 2 Different representations of high-valent iron–oxo entities: form **A** with a double Fe–O bond and form **B** with a diradical and a single Fe–O bond (for a discussion on these two different electronic configurations of iron–oxo species, see ref. 13). X = anionic axial ligand.

center and the oxygen atom). So, the ground state of the high-valent iron–oxo species of cytochrome P-450 will ressemble the diradical Fe^{IV}–O· (for **B**) whereas Fe^{V}=O with a formal double bond (form **A**) represents an excited state. However, Schwarz and coworkers have recently proposed that both states of the perferryl entity will be involved in catalytic hydroxylations, with a spin inversion during the reaction.[13]

The high-valent iron–oxo species of Cpd I of peroxidases (horseradish peroxidase HRP, ligninase, . . . *etc.*) has a lifetime which is long enough to allow the collection of physical data by different methods: UV–VIS, EPR, magnetism, resonance Raman, X-ray absorption and Mössbauer.[2] All these different methods confirmed that Cpd I of horseradish peroxidase is a perferryl species with a radical-cation on the porphyrin ligand $(Por^{\cdot+})Fe^{IV}$=O. X-Ray absorption[15] and resonance Raman[16] studies respectively indicated that the Fe=O bond distance was 1.6 Å with a vibration at 737 cm^{-1}. The π-radical-cation of Cpd I has a predominant $^2A_{2u}$ character, indicative of an electron abstraction from the a_{2u} orbital of the porphyrin ligand.[17] This porphyrin radical is weackly ferromagnetically coupled with the spin $S = 1$ of the ferryl state.[18] It should be noted that HRP is unable to catalyze O-atom transfer reactions, in contrast to chloroperoxidase, suggesting that the lability of the high-valent iron–oxo is mainly controlled by the axial ligand (both chloroperoxidase and cytochrome P-450 have a cysteine as proximal ligand, instead of a histidine for a horseradish peroxidase).[19,20] The reduced accessibility for substrates in HRP can not be the only factor to explain the absence of oxygenation activity for this enzyme, since the amino acids of the distal site responsible for the heterolytic cleavage of the peroxidic O–O bond are not oxidized during the catalytic cycle of HRP despite their close interactions with the active site.

Since the pioneering work of Groves *et al.*[3] on the characterisation of an iron(IV)–oxo radical-cation porphyrin complex, many groups have focused their efforts on the isolation and the description of chemical models of heme-enzymes. In all these model systems, the exchange between the spin $S = 1$ of the ferryl group with the spin $S' = 1/2$ of the porphyrin radical-cation was found to be strongly ferromagnetic in contrast to the weak ferromagnetic coupling usually observed with Cpd I derivatives.[21] The one-electron reduced complex, namely $(Por)Fe^{IV}$=O equivalent to a peroxidase Cpd II, which was described early in the cases of six-coordinate[22*a*] and five-coordinate[22*b*] porphyrin complexes, can be isolated by a reductive chromatography of $(Por^{\cdot+})Fe^{IV}$=O over basic alumina and is stable at room temperature.[22*c*] A $(Por)Mn^{IV}$=O complex has been characterised by X-ray absorption spectroscopy.[23] The Mn–O bond distance is 1.69 Å and the complex has a $S = 3/2$ spin state corresponding to a high spin d^3 configuration. Recently, it has been reported the detection and the characterization of a manganese(V)–oxo porphyrin complex by rapid-mixing stopped-flow spectrophotometry.[24]

High-valent iron–oxo complexes can be prepared with peracids *via* the intermediate formation of a acylperoxo–iron(III) porphyrin complex. This latter compound undergoes a heterolytic cleavage of the O–O bond in dichloromethane to provide the iron–oxo or a homolytic cleavage in toluene to give rise to a bridged *N*-oxide porphyrin.[25] It must be noted that all the high-valent metal–oxo porphyrin complexes are highly electrophilic and as such react with alkanes, alkenes or heteroatoms in contrast to the nucleophilic $(Por)Fe^{III}$–OOH complexes[26] (see also ref. 27 for the use of thianthrene-5-oxide as a probe to distinguish between electrophilic and nucleophilic oxidants).

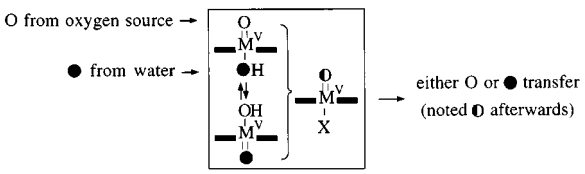
The stability of high-valent iron– or manganese–oxo species is highly dependent on the nature of the ligands. An inert d^2 square-pyramidal manganese(V)–oxo stable at room temperature has been prepared with a diamido ligand[28] (see also ref. 29 for the design of robust ligands for oxidizing complexes). An additional example of lability *versus* stability of high-valent species is the case of nitrido–manganese(V) porphyrin complexes which is kinetically inert with organic substrates, but able to transfer the nitrido motif to chromium(III) porphyrin *via* a two-electron redox process mediated by a heterobimetallic μ-nitrido intermediate.[30] The same nitrido–manganese(V) porphyrin complexes can be transformed into nitrogen atom-transfer agents after acylation of the nitrido ligand to generate a labile acylimido–manganese(V) porphyrin complex.[31]

At the present stage of knowledge, the design of metal–oxo complexes able to efficiently catalyse oxygenations is still challenging, since all the parameters involved in the different O-atom transfer steps are not fully understood.

A new type of tautomerism: the oxo–hydroxo tautomerism

After the above reminders on high-valent metal-oxo porphyrin complexes, we wish now to report the recent discovery of an oxo–hydroxo tautomerism[32,33] and its utilisation as mechanistic tool in oxygenation reactions catalysed by water-soluble metalloporphyrins.

Using isotopically labelled oxidants or labelled water, it has been shown that the oxygen of the metal–oxo porphyrin complex can be quickly exchanged with water *via* the axial hydroxo ligand with reaction rates depending on the experimental conditions (pH, temperature, composition of the medium, nature of the axial ligands, . . .). We shall see that, using the label distribution in oxidation products modulated by this oxo–hydroxo tautomerism, it is possible to unambiguously distinguish between oxygenation reactions occurring *via* an oxygen transfer from a high-valent metal–oxo complex or *via* an autoxidation mechanism (see ref. 34 for a review on this controversial debate) in metalloporphyrin-catalysed oxygenations carried out in the presence of $H_2{}^{18}O$. For short, the phenomenon termed oxo–hydroxo tautomerism corresponds to a rapid shift of two electrons and one proton from a hydroxo ligand (electron-rich ligand) to the *trans* oxo species (electron-poor ligand) leading to the transformation of the hydroxo ligand into an electrophilic oxo entity on the opposite side of the initial oxo (Scheme 3). The main consequence of this tautomerism is the incorporation within the substrate of an oxygen atom coming from either the oxidant or from bulk water, respectively in the ratio 1 : 1. the degree of ^{18}O-exchange observed into the product (epoxide, alcohol, . . .) is then mechanistically informative.



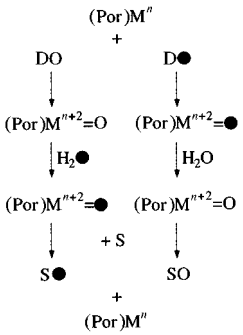
Scheme 3 The oxo–hydroxo tautomerism mediates the incorporation into the oxidation product of 50% of oxygen coming from the primary oxidant and 50% from water. X = hydroxo ligand.

Some previous data on O-exchange of metal–oxo species with bulk water

In the last fifteen years, several reports mentioned the use of ^{18}O-labelling experiments in order to characterize high-valent

metal–oxo species or to elucidate the mechanism of O-transfer by these reactive species. For reactions performed in the presence of water, results varied from 0 to 100% of O-incorporation form water, depending on the experimental conditions. Most of these results can be understood by reference to the oxo–hydroxo tautomerism (for detailed comments, see the paragraph on required conditions to observe oxo–hydroxo tautomerism) or on the basis of a direct O-exchange of the oxo ligand with the bulk water.

Most of the studies to determine the origin of the incorporated oxygen atom in alkene epoxidations or alkane hydroxylation catalysed by metalloporphyrins have been performed in organic solvents or biphasic media with hydrophobic complexes. From these data, it has been concluded that the oxygen atom originated from the primary oxidant (PhIO,[35] LiOCl,[36] $KHSO_5$[37]). When experiments are performed in water or in an organic solvent containing a sufficient amount of water, several reports suggested that high-valent metal–oxo complexes exchanged the coordinated oxygen atom with water (using either labelled water or labelled oxygen atom donor). As indicated in Scheme 4 for a theoretical 100% O-exchange with water, these



Scheme 4 Principle of labelling studies: case of theoretical 100% O-exchange with water. Unlabelled or ^{18}O-labelled water (H_2O and H_2●) and oxygen atom donor (DO and D●). [Por] = porphyrin ligand; S = substrate.

experiments were usually based on generating the active species with ^{18}O-labelled activating agent [H_2O_2; *m*-chloroperoxybenzoic acid (*m*-CPBA); O_2 in the presence of a reductant] and washing the label in the presence of unlabelled water, or at the reverse, using unlabelled oxidant and performing the reaction in ^{18}O-labelled water.

Resonance Raman investigations on Cpd II of HRP at pH 7, based on isotopic shift of the Fe^{IV}=O stretching mode of Cpd II ($\nu_{Fe=O}$ was observed at 774 cm^{-1} after activation with either $H_2{}^{16}O_2$ or $H_2{}^{18}O_2$ in $H_2{}^{16}O$, at 740 cm^{-1} for activation with either $H_2{}^{16}O_2$ or $H_2{}^{18}O_2$ in $H_2{}^{18}O$), provided evidence for the oxygen atom exchange between the heme-Fe^{IV}=O and bulk water (Table 1).[38] In a controversial manner, this exchange was

Table 1 Resonance Raman data on the possible exchange of the oxygen atom of high-valent metal–oxo species with bulk water

	$\nu_{M=^{16}O}$/ cm^{-1}	$\nu_{M=^{18}O}$/ cm^{-1}	Exchange	Ref.
Fe^{IV}=O (HRP Cpd II)	774	740	Yes	38
Fe^{IV}=O (diacetylheme HRP Cpd II)	781	745	No	39
Mn^{IV}=O (Mn subst HRP Cpd II)	626	596	No	39
$(Por^{\cdot+})Fe^{IV}$=O (TMP)	828	792	No	40

not observed in the case of stable species of diacetylheme or manganese substituted HRP: the Raman spectrum of Cpd II generated with $H_2{}^{16}O_2$ or $H2^{18}O_2$ presented lines at 781 or 745 cm^{-1} (diacetylheme HRP), at 626 or 596 cm^{-1} (Mn–HRP), respectively. No isotope-induced change was observed at neutral pH for 1 h at 4 °C in the presence of $H_2{}^{16}O$ or $H_2{}^{18}O$, indicating no appreciable exchange of the oxo entity with bulk water.[39] In studies performed at −80 °C on a ferryl porphyrin π-cation-radical derived from the synthetic (*meso*-tetramesitylporphyrinato)iron(III) chloride [(TMP)Fe^{III}Cl], the $\nu_{Fe=O}$ band was observed at 828 cm^{-1} (activation with [^{16}O]*m*-CPBA) or 792 cm^{-1} (activation with [^{18}O]*m*-CPBA), the first one remaining unshifted in the presence of $H_2{}^{18}O$; therefore the oxo oxygen atom was not easily exchanged with water under these conditions (Table 1).[40]

The O-exchange of metal–oxo with bulk water can also be monitored by analysing the label content of oxygenation products of reactions catalysed by synthetic metalloporphyrins. Groves *et al.*[3] reported that the high-valent iron–oxo complex generated in a first step from (TMP)Fe^{III}Cl with *m*-CPBA in an organic medium containing 1% $H_2{}^{18}O$ was able, in a second step, to epoxidize norbornene with a 99% ^{18}O-incorporation. This result allowed to discard the hypothesis of either free or metal coordinated peroxyacid as the oxygen transfer agent and support an high-valent iron–oxo intermediate with an oxygen exchangeable with added $H_2{}^{18}O_2$. Incorporation of ^{18}O from bulk water was further noticed[41] in the course of epoxidation of β-methylstyrene by manganese(V)–oxo porphyrin in CH_2Cl_2 saturated in $H_2{}^{18}O$, indicating here also a rather fast exchange of the oxo ligand with water. This ^{18}O-exchange was clearly slower in the case of manganese(IV) species and was inhibited by the presence of pyridine as axial ligand.[41,42]

Oxo-hydroxo tautomerism with water-soluble metalloporphyrins

Epoxidation reaction

We initially reported oxo–hydroxo tautomerism to explain isotopic results observed in aqueous phase during $KHSO_5$ epoxidation of carbamazepine (CBZ), an analgesic and anticonvulsivant drug, catalysed by a cationic water-soluble manganese porphyrin.[33] In such reaction performed at pH 5 in aqueous solution with various contents of $H_2{}^{18}O$, it was shown that half of the oxygen atoms incorporated in the epoxide came from the solvent (Fig. 1(*a*)]. It was checked that neither CBZ-

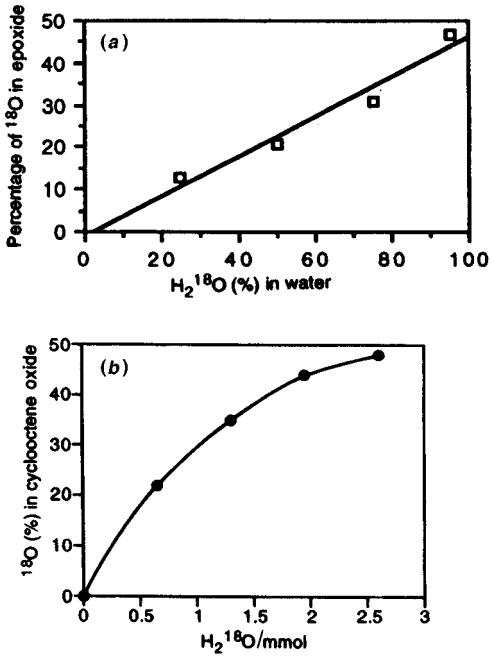
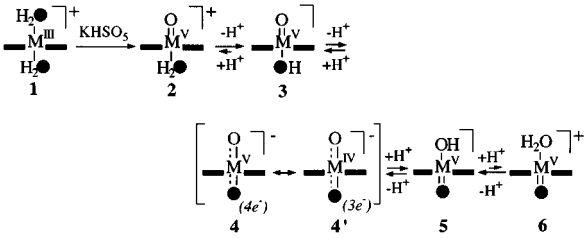


Fig. 1 (*a*) The amount of labelled oxygen found in CBZ oxide correlates with half the content of ^{18}O-label of water present in the reaction mixture. In abscisse: content (%) of $H_2{}^{18}O$ in water (from ref. 33 with permission from the American Chemical Society; see also ref. 44 for a similar correlation). (*b*) Dependence on a sufficient concentration of water in non-aqueous solvent to observe oxo-hydroxo tautomerism. In abscisse: 0.5, 1.0, 1.5, 2.0 and 2.5 mmol of $H_2{}^{18}O$ correspond to 1, 2, 3, 4 and 5 M $H_2{}^{18}O$ concentration, respectively; substrate concentration was 20 mM (from ref. 44 with permission from the American Chemical Society).

oxide[33] nor $KHSO_5$[37,43] exchanged oxygen atoms with water in the reaction conditions.

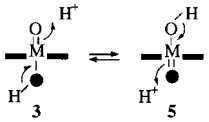
To explain the constant ratio of 0.5 for the incorporation of oxygen from the solvent, we proposed an oxo–hydroxo tautomerism mechanism[32] (formerly named 'redox tautomerism' in refs. 33, 43–47) involving a coordinated water molecule on the manganese(III) porphyrin precursor **1** (Scheme 5). It must



Scheme 5 General scheme for the oxo–hydroxo tautomerism

be noted that a 50% O-exchange corresponds only to the oxo–hydroxo tautomerism involving the hydroxo ligand *trans* to the high-valent metal–oxo complex, but not to a direct exchange of the oxo ligand with bulk water.

Mn(TMPyP), the pentaacetate of the diaquamanganese(III) derivative of *meso*-tetrakis(1-methyl-pyridinium-4-yl)porphyrin, can exist in aqueous medium with one or two metal-bound water molecules as axial ligands (**1** in Scheme 5; see ref. 48 for a X-ray structure of the bis-aqua-MnTMPyP complex). Increasing the metal oxidation state from III to V (going from the Mn^{III} complex **1** to the Mn^{V}=O **2**) should lower sufficiently the pK_a value of the ligated water to allow, at the pH of the reaction, its conversion into a hydroxo ligand (**3**; see ref. 49 for a discussion on the pK_a values of aqua and hydroxo ligands in high-valent metalloporphyrins). Removal of a proton from this hydroxo ligands results in the formation of the stabilized anion **4** with four electrons delocalized on both metal–oxygen bonds (**4′** is a mesomeric form with three delocalized electrons and manganese in the formal oxidation state IV). This anion can be protonated with the same probability at the end of one of the two metal–oxo-like bonds, giving rise to either form **3** or **5**, which reacts with CBZ to produce CBZ-oxide containing either ^{16}O or ^{18}O, respectively, in the ratio 1 : 1. The conversion of **3** to **5** does not necessarily involve **4** and **4′** as discrete deprotonated intermediates but might also proceed *via* a hydrogen-bonded water molecule in a more concerted fashion (Scheme 6).

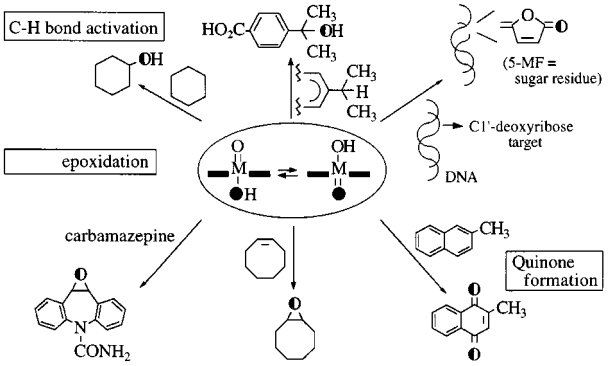


Scheme 6 Key step of the oxo–hydroxo tautomerism

Other recent reports support the concept of oxo–hydroxo tautomerism.[24,44,47] Groves *et al.*[24] reported also the ^{18}O-incorporation in CBZ-oxide in a Mn(TMPyP)-catalysed oxidation of CBZ *via* an oxo–hydroxo interconversion. Lee and Nam described similar ^{18}O-incorporation in cyclooctene epoxidation by either *m*-CPBA, H_2O_2 or Bu^tOOH catalysed by [*meso*-tetrakis(pentafluorophenyl)porphyrinato]iron(III) chloride $Fe^{III}(F_{20}TPP)Cl$, the reaction being performed in a MeOH–CH_2Cl_2 mixture containing 10% H_2O.[44] Even at low pH values, CBZ epoxidation data obtained in aqueous solutions by H_2O_2, Bu^tOOH or $KHSO_5$ in the presence of [*meso*-tetrakis(2,6-dichloro-3-sulfonatophenyl)porphyrinato]iron(III) chloride indicated that the oxo–hydroxo tautomerism was involved.[47] In these latter cases, the experiment strongly supported that a common high-valent iron–oxo species was generated from the different oxidants and was the reactive intermediate responsible for alkene epoxidation.

Hydroxylation reactions (Scheme 7)

The oxo–hydroxo tautomerism was further characterized in the oxidation of deoxyribose C–H bonds of DNA by the Mn(TMPyP)–$KHSO_5$ system.[45] Hydroxylation at carbon-1′ of



Scheme 7 Examples of oxo–hydroxo tautomerism from literature data. ○: unlabelled oxygen; ●: labelled oxygen; ◐: mixed labelled oxygen.

deoxyribose gave in several steps 5-methylene-2-furanone (5-MF), as final sugar residue. In the presence of labelled $H_2{}^{18}O$, 50% of oxygen coming from the primary oxidant (^{16}O from $KHSO_5$) and 50% from the solvent (^{18}O from $H_2{}^{18}O$) were incorporated in 5-MF, strongly supporting a metal–oxo mediated DNA cleavage with an oxo–hydroxo tautomerism to explain the ^{18}O-incorporation in the desoxyribose oxidation product. Another example came from the monopersulfate oxidation of 4-isopropylbenzoic acid performed in $H_2{}^{18}O$ and catalysed by the same water-soluble metalloporphyrin Mn(TMPyP).[43] In the primary hydroxylation product, 4-(1-hydroxy-1-methylethyl)benzoic acid, nearly half of the oxygen atoms incorporated in the alcohol function came from water. In the cyclohexane hydroxylation by *m*-CPBA catalysed by $Fe(F_{20}TPP)Cl$, the percentage of ^{18}O incorporated in cyclohexanol was also found to be close to 50%, with a reaction mixture containing only 10% of water.[44]

Quinone formation (Scheme 7)

In an aqueous solution the metalloporphyrin-catalysed oxidation of 2-methylnaphthalene to *p*-quinones involves two consecutive oxygen transfers from an intermediate metal–oxo entity responsible for 30 to 55% indirect incorporation of ^{18}O from water into the generated quinones.[46]

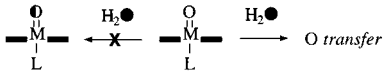
Required conditions to observed oxo-hydroxo tautomerism

An axial ligand competitive to the hydroxo ligand inhibits oxo–hydroxo tautomerism

In heme-enzymes, the presence of a cysteinato ligand (cytochrome P-450 or chloroperoxidase) or an imidazole from an histidine (peroxidase) prevents water from coordinating to iron. This implies that there is no possible exchange between high valent metal–oxo intermediates and water through an oxo–hydroxo tautomerism. From this point of view, the experimental data presented above in Table 1 on Cpd II of HRP is rather controversial and suggests that an exchange of the oxygen of the metal-oxo with bulk water on the distal side may occur in some conditions (probably *via* a *cis*-dihydroxo complex and not *via* a prototropy betwen the metal–oxo oxygen and the hydroxo ligand as in the oxo–hydroxo tautomerism).

With synthetic metalloporphyrins the situation is different. Iron and manganese porphyrins are known to form imidazole and pyridine complexes when these heterocycles are present in reaction mixtures. In the epoxidation of *cis*-β-methylstyrene with *m*-CPBA catalysed by $Mn^{III}(TMP)Cl$, the presence of pyridine completely prevents isotopic enrichment of epoxide products when the reaction is performed in the presence of

$H_2{}^{18}O$.[41] In the epoxidation of cyclooctene by Fe(F_{20}TPP)Cl and H_2O_2, it was found that effectively the ^{18}O-incorporation into the product diminished as the amount of 5-chloro-1-methylimidazole added to the reaction mixture increased.[44] So when the axial position opposition to the oxo group is blocked by a ligand (not derived from water), the oxo–hydroxo tautomerism cannot occur and consequently the oxygen incorporated in the oxidation product is 100% from the oxidant, instead of 50% from the oxidant and 50% from water (Scheme 8).

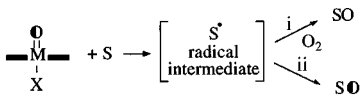


Scheme 8 Inhibition of the oxo–hydroxo tautomerism equilibrium in the presence of strong axial ligands. L = neutral ligand, *e.g.* pyridine or imidazole.

When there is no *trans* ligand, evidently the oxo–hydroxo tautomerism does not occur. But, when the *trans* ligand is a water molecule instead of an hydroxo ligand [see hereafter for a discussion on the case of metal(IV)–oxo species], the tautomerism is largely reduced. This may be an explanation why the oxo–hydroxo tautomerism was not observed during the oxidation of polycyclic aromatic hydrocarbons catalysed by iron tetrasulfophthalocyanine performed in the presence of $H_2{}^{18}O$ (the reactive species was shown to be Fe^{IV}=O)[50] or in cobalt-mediated alkene epoxidations with potassium monopersulfate[51] where the oxygen atom was coming only from the oxidant.

Competitive autoxidation route lowers incorporation of oxygen from water

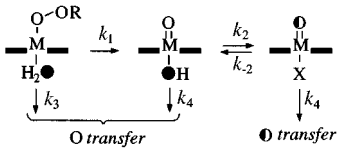
Groves *et al.* noticed that during cyclooctene[41] or *cis*-β-methylstyrene[42] epoxidation by manganese(IV)–oxo porphyrin under aerobic conditions, dioxygen was intimately involved in the oxidation process with oxidation products partially resulting from an autoxidation process. Evidently, the consequence is a lowering in isotopic enrichment from solvent. During the monopersulfate oxidation of ketoprofen catalysed by Mn(TMPyP),[43] trapping of radical intermediates by molecular oxygen (route i, Scheme 9) was shown to compete with the oxygen rebound mechanism (route ii), explaining the observed reduction of ^{18}O-incorporation from solvent in the final product when ketoprofen was oxidised under air by the system Mn(TMPyP)–$KHSO_5$–$H_2{}^{18}O$ system.



Scheme 9 Diverted autoxidation route lowers the oxygen incorporation rate. Route i: radical escaping from the solvent cage (autoxidation route); route ii: recombination within solvent cage (oxygen rebound mechanism).

Temperature effect

In order to characterize the high-valent reactive species formed by oxidative activation of metalloporphyrins, many experiments have been performed at low temperature with some of them concerning ^{18}O-incorporation into the products in the presence of $H_2{}^{18}O$. In the more extensive study, Lee and Nam[44] described the cyclooctene epoxidation by H_2O_2 or *m*-CPBA in the presence of Fe(F_{20}TPP)Cl at different temperatures. The ^{18}O-enrichment in the epoxide gradually increased as the reaction temperature raised from −78 to 45 °C. The authors suggested that an Fe^{III}–OOR species was involved at low temperature, with a rate of the O–O bond cleavage (leading to the high-valent iron–oxo porphyrin complex) lower than the oxygen atom transfer rate ($k_1 < k_3$ in Scheme 10). At higher

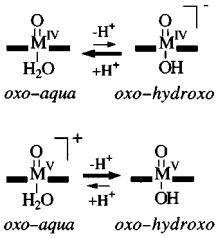


Scheme 10 Kinetic parameters depending on temperature. X = hydroxo ligand.

temperature the formation of the high-valent iron oxo porphyrin should be favored (increase of k_1). However, since tautomerism is a phenomenon highly dependent on temperature, the present results might alternatively be re-interpreted as a fast formation of the iron–oxo species ($k_1 > k_3$), even at low temperature, but with a slow prototropy ($k_2 < k_4$) at this teperature and a faster one ($k_2 > k_4$) at higher temperature (k_3 and k_4 = oxygen atom transfer rates; the best conditions to observe the oxo–hydroxo tautomerism correspond to $k_1 > k_3$ and $k_2 > k_4$). We must note that even at low temperature (−78 °C) iron–oxo porphyrin species have been detected and characterized.[3,21,22]

Differences in exchange kinetics for metal(IV)–oxo and metal(V)–oxo

From experiments conducted on *cis*-β-methylstyrene with manganese(V)–oxo and manganese(IV)–oxo porphyrin complexes, Groves *et al.* concluded from the ^{18}O results that, in addition to differences in oxygen transfer occurring with retention or loss of the stereochemistry, the manganese(IV)–oxo slowly exchanged its oxo ligand with $H_2{}^{18}O$, while the exchange was very fast for the manganese(V)–oxo complex.[41] These data are consistent with Schemes 5 and 11 and with



Scheme 11 Equilibria between oxo–aqua and oxo–hydroxo forms depending on the oxidation state of the metal center

literature data on the proton acidity of coordinated water in high-valent species:[49,52,53] going from **3** to **5** only needs a prototropy in the case of a manganese(V)–oxo species (Scheme 5 and 11; the oxo–hydroxo is the major form), whereas in the case of manganese(IV)–oxo (Scheme 11) the ligand *trans* to the oxo is mainly a water molecule owing to the lower acidity of the ligated water when the metal oxidation state is reduced. So, for manganese(IV)–oxo complexes, the oxo–hydroxo tautomerism can only affect the small fraction of metal–oxo species with an hydroxo ligand, the oxo–aqua form being dominant in this case.

Role of the ratio water/substrate concentrations

The percentage of ^{18}O incorporated in oxidation products might be governed by the relative rate to reach the tautomerism equilibrium (k_2 in Scheme 10) which is a function of the water concentration, and the rate of oxygen transfer (k_4) which depends on the substrate concentration. For reaction performed in an essentially aqueous medium (a 90% aqueous solution is 50 M in water) and a substrate rather diluted (*e.g.* 1 mM), the competition between the tautomerism and the oxygen transfer was not observed: the water/substrate molar ratio ($\approx 5 \times 10^4$) was largely in favor of the oxo–hydroxo tautomerism.[33] In an organic medium containing only a small amount of water and at high substrate concentrations, the situation is opposite and can affect the tautomerism equilibrium and consequently the level of ^{18}O-incorporation.[44] An example of such an extreme

condition concerns the epoxidation of 1 M cyclohexene solution in CH_2Cl_2–MeOH containing 5% of $H_2{}^{18}O$ with a metalloporphyrin catalyst and H_2O_2, Bu^{t}OOH or *m*-CPBA as oxygen donor. In these conditions, no ^{18}O-incorporation was observed in the epoxide (water/substrate molar ratio ≈ 3).[35] In intermediate conditions, such as in epoxidation of 20 mM cyclooctene with H_2O_2 catalysed by Fe(F_{20}TPP)Cl in an organic medium containing increasing amounts of water, the 50% O-incorporation from water was observed for a reaction mixture containing at least 10% of water [water/substrate molar ratio above 250; Fig. 1(*b*)].[44] In the rare case of a very small concentration of substrate, then the reaction becomes very slow and the aqua ligand (form **2** or **6** in Scheme 5) can exchange with water from solvent and the ^{18}O incorporation from solvent can raise above 50%.[44]

Other parameters to take into account

Probably several other parameters may influence the oxo–hydroxo tautomerism but no systematic study has been done up to now. Among them, the pH value of the reaction mixture plays surely a key role in this prototropy mechanism as also the nature of the metal and the ligand in the metalloporphyrins through their capacity to form differently coordinated complexes. In addition, some reported variations of the ^{18}O rate of incorporation around 50% suggest that the oxo-hydroxo tautomerism equilibrium is probably tuned by small variations of kinetic parameters, including solvent effect or differences in the kinetic parameters of the oxygen transfer from the metal–oxo to the substrate.

Conclusion

Among the different methods to study the mechanism of oxidation mediated by high-valent metal–oxo complexes, the recent discovery of the 'oxo–hydroxo tautomerism' provides an additional useful tool to discuss the mechanism of catalytic O-atom transfer reactions, the nature of the axial ligand *trans* to the oxo species and the oxidation state of these metal–oxo entities. In particular, when the required conditions to observe the oxo–hydroxo tautomerism are respected, it appears that the incorporation into the oxidation product of 50% of oxygen coming from water constitutes a strong evidence of an oxygen atom transfer involving an high-valent metal–oxo intermediate.

In the future, it might be possible to generalize this oxo–hydroxo tautomerism to other complexes having both the oxo and hydroxo ligands in a *trans* configuration as reported in the present survey for water-soluble metalloporphyrins but also for complexes having these two ligands in a *cis* configuration.

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Jean Bernadou was born in Villefranche-de-Rouergue (France) in 1947, and studied Chemistry, Pharmacy (Doctorate in Pharmaceutical Sciences in 1975) and Medicine (Doctorate in 1985) at the University Paul Sabatier of Toulouse, where he was appointed Professor of Medicinal Chemistry in 1987. His collaboration with the group of Bernard Meunier started in 1980 with his research interests in the mechanism of action of antitumor drugs. He is currently working on biological applications of metalloporphyrins, in particular oxidative DNA cleavage, biomimetic oxidation of drugs and characterization of reactive metal–oxo intermediates.

Bernard Meunier was born in 1947 and educated at the Universities of Poitiers (BSc), Montpellier (with R. J. P. Corriu) and Orsay (with H. Felkin, ICSN-CNRS). After a post-doctorate at the University of Oxford, he joined the Laboratoire de Chimie de Coordination du CNRS in Toulouse in 1979. His current research interests include catalytic oxidations, oxidative DNA cleavage, oxidation of pollutants and the mechanism of action of artemisinin derivatives. He is the author of more than 210 publications and patents.

Notes and References

† E-mail: bernadou@lcc-toulouse.fr or bmeunier@lcc-toulouse.fr

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