The Influence of Structural Parameters on the Reactivity of Model Complexes for Compound II: A Mini Review

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Abstract The present brief review aims at elucidation of the parameters affecting the properties and reactivity of high valent iron(IV) oxo porphyrin complexes, being models of compound II reactive intermediate known from biochemistry of cytochromes and peroxidases. The stress is put on the influence of the axial ligand and porphyrin ring substituents, with special attention on implications for their catalytic activity.

Keywords Compound II (Cpd II) · Oxidation · Bio-mimetic catalysis

1 Introduction

Heme moiety, a naturally occurring iron porphyrin, constitutes an active site of numerous enzymes, whose main functions include binding and transport of gases, electron transfer and catalysis. Biochemical studies show that the heme active group exhibit different reactivity, depending on its immediate surrounding [1, 2]. A number of factors are usually invoked which determine the activity of heme proteins, such as axial ligation (often referred to as proximal groups), presence of aminoacids inside a distal pocket (which may participate in binding, activation and transformation of substrates), substrate binding sites etc. [3–5].

Further, the activity of the heme group in catalysis is strictly related to the ability to transform its central ion into so-called high-valent species with an oxo ligand (=O)

attached. The oxidation reaction comprises then a transfer of the oxo ligand to the substrate and an acceptance of electrons by the electron-deficient iron ion. For a long time, the highest reactivity was ascribed to iron(IV)-oxo cation radical porphyrin species, called compound I (Cpd I) [6–17]. Only recently, its one electron reduced form, iron(IV)-oxo porphyrin (compound II, Cpd II—see Fig. 1), has been proved to play a similar role in catalytic reactions, in particular in activation of C–H bond [18–20]. It should be born in mind that when the reactivity of model complexes for the reactive intermediates in hemoprotein catalysis was compared (hydroperoxo iron(III) porphyrin—Cpd 0, Cpd I and Cpd II), Cpd II appeared the most efficient in hydride-transfer [21].

The elucidation of structure–activity relationship for high-valent iron-oxo species was considerably accelerated by the ability to synthesize their mimics. Model studies in solution facilitated determination of parameters, which are the most relevant for their action in enzymatic systems. The first syntheses of Cpd II mimics were reported in early 1980s [22, 23]. The addition of a nitrogen base (*N*-methylimidazole, pyridine, piperidine) to the μ -peroxo bis iron(III) porphyrin [TmTPFe-O₂-FeTmTP] (TmTP—dianion of *meso*-tetra-*m*-tolylporphyrin) at –80 °C in toluene solution resulted in the formation of [BTmTPFe(IV)=O] species (B—nitrogen base), as proved by ¹H NMR and UV–VIS. The iron(IV)-oxo species might also be generated by addition of hydrogen peroxide to the iron(III) porphyrin complex—[meso-tetrakis(2,4,6-trimethyl-3-sulfonatophenyl)porphinato]iron(III) hydroxide (tetrasodium salt) at pH 10.0 in buffered aqueous solution [24]. It was proved that Fe(IV)=O porphyrins might also be obtained through electrochemical oxidation of porphyrin, although the main product was Fe(IV)=O porphyrin cation radical, Cpd I mimic [25]. Since then, other porphyrin substrates have been used to yield synthetic Cpd II mimics

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Fig. 1 Schematic view of Cpd I and Cpd II

[26], allowing for their physico-chemical characterization and further studies of their reactivity.

Following the experimental findings, theoretical investigations of the molecular mechanisms of oxygenations by high valent oxo-iron complexes concern mostly Cpd I systems (see e.g. [8, 14, 27–30]), while studies of the reactivity of Cpd II models are rather scarce [31–33] and mostly focus on the reactivity of cytochromes, in which the central iron ion is coordinated by a thiolate ligand from cysteine. The structure and reactivity of high valent iron-oxo species has been already reviewed, but the main stress is always put on the Cpd I parameters [8, 34–36].

Our aim, therefore, is to investigate how parameters of the synthetic models for Cpd II, in particular porphyrin ring substitution and type of axial ligand, affect their structure and reactivity. Our motivation arises from the fact that the physical parameters of Cpd II determine its catalytic activity, especially in C–H bond activation in hydroxylation and dehydrogenation processes [37].

2 Influence of Axial Ligand on Parameters of Cpd II Model Complexes

It appears that the main structural difference in heme enzymes is connected with the nature of an amino acid

coordinated in the proximal position to the iron(III) center in the active site (i.e. tyrosine for catalases, histidine for peroxidases and cysteine for cytochrome P450). Consequently, the model experimental and theoretical studies focused mostly on elucidation of the influence of the axial ligand on the structure and hence catalytic reactivity of iron porphyrins (Fig. 2). In the first instance, they aimed at understanding the activity of hemoproteins.

Antony et al. [38] studied the influence of the axial ligand (Cl^- , Im, $-\text{SCH}_3$) on the structural parameters of high-valent iron oxo intermediates as models of active species in chloroperoxidases, peroxidases and cytochromes P450, respectively. Their theoretical DFT-LDA calculations performed within SCC-X α method showed that the charge and spin density distribution in the Fe(IV)=O group are insensitive on the type of axial ligand. However, axial ligation affects the polarity of the Fe(IV)=O fragment.

More recently, Sun et al. [33] investigated a series of neutral N-donor ligands (imidazole, pyridine and their derivatives) as ligands in $[(\text{L})\text{PFe(IV)=O}]$ by means of DFT-B3LYP method. Their conclusions supported earlier observation that axial ligation resulted in the weakening of the Fe(IV)=O bond expressed by the elongation of Fe(IV)=O distance and movement of Fe ion into the porphyrin plane.

The obtained results were rationalized in terms of the electrophilic parameters of the chosen axial ligands consisting of a series of substituted pyridines with groups of varying Hammet constants. The comparison revealed that when the electron-withdrawing ability of the axial ligand was increased, the Fe(IV)=O bond became shorter [33]. At the same time, the Fe-axial ligand was elongated. Both changes resulted in the decrease of the Fe(IV)=O bond strength.

Additionally, the Fe(IV)=O electron density in complexes with axial ligands were lower than in the five-coordinate $[\text{PFe(IV)=O}]$. In such a way the electron density

Fig. 2 Influence of the type of axial ligand on the parameters of Cpd II models

Fig. 3 Changes in reactivity of Cpd II models caused by axial ligation

was shifted from oxygen to iron ion and the porphyrin ligand and Fe(IV)=O bond became less polar.

This finding confirmed conclusions from the earlier experimental studies by Gold et al. [39], in which a series of [(L)(TPP(2,6-Cl))Fe(IV)=O] complexes (TPP(2,6-Cl)—dianion of mezo-tetrakis-2,6 dichlorophenyl porphyrin) with axial ligands being solvent molecules of tetrahydrofuran, dimethylformamide or 1-methylimidazole. They demonstrated that the strengthening of Fe-axial ligand bond weakened the Fe(IV)=O bond. The effect was ascribed either to a trans effect or by movement of the iron ion toward the porphyrin plane.

Finally, the strengthening of the Fe-axial ligand bond results also in the decrease of Fe(IV)=O stretching frequency, as shown by resonance Raman spectra [38].

2.1 Implications for Catalysis

The above mentioned studies showed that the changes in axial ligation of model Cpd II complexes influence the Fe(IV)=O group, mostly its length and polarity (see Fig. 2). It is of no surprise that this change would be reflected in the rate and mechanism of reactions, which they catalyse.

In order to assess the differences in the reactivity of Cpd II models two concurrent catalytic processes (epoxidation and dehydrogenation of 1,3-cyclohexadiene) were studied for complexes with different axial ligands (none, imidazole, pyridine, 4-amino-pyridine, and 4-nitryl pyridine) with DFT/B3LYP method [33]. The selectivity of the reaction may be switched upon ligation, as shown by comparing the barriers of the rate-determining steps of both processes. The un-ligated system clearly favoured epoxidation, whereas dehydrogenation and epoxidation were practically equally probable (the barriers for dehydrogenation and

epoxidation were within the error limit of the performed calculations)—see Fig. 3. As the axial ligand was varied, the barrier heights were quite small (differences in energies amounted to 3.6 and 3.3 kcal/mol for dehydrogenation and epoxidation, respectively), suggesting only minor axial ligand effect on the reactivity of Cpd II mimics. The longer Fe(IV)=O bond was (and the more electron-withdrawing substituent in axial ligand), the larger both barriers were, but the changes were not very pronounced, as mentioned earlier.

Similar conclusions were drawn from a Car-Parinello molecular dynamics (within B3LYP and BP86) investigation of O–H bond cleavage in OOH^- by Cpd II, where active sites of peroxidases and catalases were modelled as [(L)PFe–OH] species (L—imidazole or phenolate interacting with arginine, respectively) [40]. The energy barriers for O–H abstraction were invariant in respect to the axial ligand. One should note, however, that the active site in this study consisted of iron-hydroxo group, as is often postulated for peroxidases [41].

Moreover, there is no significant influence of the nature of the axial ligand on the reactivity of Cpd II mimic in oxidations of 4-methoxybenzyl alcohol and 4-methoxybenzaldehyde, as confirmed both by theoretical (DFT with B3LYP) and experimental kinetic studies [24].

Another important aspect of the catalytic reaction was brought about by theoretical considerations on methane hydroxylation [31]. In the comparative study, two Cpd II models were employed: [PFe(IV)=O] and [(SH)PFe(IV)=O] $^-$. It was shown that the un-ligated Cpd II model exhibited so called *two-state reactivity* model (TSR)—it underwent spin-crossing along the reaction pathway. While the starting state was triplet, the C–H bond activation proceeded on the quintet surface. The presence of the axial ligand altered the reactivity, so that the system

did not change multiplicity and stayed on the triplet surface (compare Fig. 3). Two state reactivity mechanism was also postulated to operate during cyclohexane oxidation to adipic acid by $[\text{PFe(IV)=O}]$, as studied by DFT with B3LYP functional [42].

The detailed analysis of the Cpd II mimic frontier orbitals [31] revealed that C–H bond activation in CH_4 may proceed through both π - and σ -attack on $[\text{PFe(IV)=O}]$, the latter mechanism was excluded for axially ligated $[(\text{SH})\text{PFe(IV)=O}]^-$. Finally, it was shown that the apparent reaction barrier for C–H abstraction was lower for the unligated system. This finding showed inversed trend as compared with the results of the H-abstraction from 1,3-cyclohexadiene, where the process was facilitated by the presence of the axial ligand [33]. The difference may arise from the different character of the axial ligands, as the neutral ones were investigated for dehydrogenation of 1,3-cyclohexadiene, as opposed to the negatively charged SH^- studied in the context of CH_4 hydroxylation.

3 Influence of Porphyrin Substituents on Cpd II

The studies of the influence of the heme substitution on the reactivity of hemeproteins (see e.g. [3] and references therein) are the foundation of the analogous studies in model systems. It follows from the statement that the electron density on the iron ion is related to the basicity of the pyrrolic nitrogen atoms of the porphyrin, which, in turn, depends on the structure and substituents of the porphyrin ligand [43].

Nam and co-workers showed that the oxidizing power of high-valent oxo porphyrin species may be adjusted by altering the electronic nature of the porphyrin ligand. In particular, an electron-deficient $[\text{TPFPPFe(IV)=O}]$ (TPFPP—dianion of *meso*-tetrakis(pentafluorophenyl)) complex was shown a reactivity comparable to that of Cpd I model [44].

The recent catalytic results on the hydroxylation of xantene by a model high valent iron oxo systems obtained from $[(4\text{-TMPyP})\text{Fe}]$ (4-TMPyP—dianion of *meso*-tetrakis(*N*-methyl-4-pyridinium porphyrin) by Bell and Groves [45] suggested that the *meso*-substitution in porphyrin ligand influenced the σ -donor properties of the coordinating pyrrole nitrogen atoms. They, in turn, affected the energies of the frontier orbitals of the Cpd II complex. It was postulated that this may tune the catalytic performance, as demonstrated for the model manganese systems [46].

Indeed, kinetic studies on the oxygenation of alkenes and benzylic alcohols by a series of chlorinated *meso*-tetrakis-phenylporphyrins were performed [47], which enabled a further insight into the macrocycle structure relation on parameters characterizing Cpd II models. The measured rate constants for oxidation reactions revealed that the more electron withdrawing substituents on the porphyrin ring, the lower catalytic activity of the examined complexes. This finding was rationalized taking into account the mechanism of the studied reactions. They were initiated by the disproportionation of Cpd II mimics into Cpd I and resting state iron(III) systems. As the former were made responsible for the proper catalytic process, in this sense the cited studies indicated that *meso*-substitution of porphyrin ligand affected Cpd II electrochemical properties.

The electrochemical properties of different porphyrin complexes, including high-valent iron-oxo species were studied by Fukuzumi [48]. Theoretical studies based on Marcus theory related redox properties of Cpd II to the planarity of the macrocycle, which is known to depend on the presence of porphyrin ring substituents (see Fig. 4) [49, 50].

Fukuzumi [48] demonstrated that the stronger binding of iron with the non-planar porphyrin upon electrochemical Fe oxidation, a larger bond reorganization energy and,

Fig. 4 Influence of the type of porphyrin substituents on the parameters of Cpd II models

consequently, a slower electron-transfer rate as compared with the planar porphyrin.

One should note that the planarity of the centre of the complex is also induced by axial ligation, as described earlier.

As is seen, further studies are needed, both by experiment and theory, to investigate in depth the reactivity pattern of Cpd II models based on substituted porphyrins.

3.1 Influence of the Porphyrin Substitution on Catalytic Properties

Little is known on the relation between the structure of the porphyrin ligand and the catalytic performance of a model Cpd II complex. The hydroxylation of alcohols and aldehydes by substituted porphyrin species, refereed to in the above paragraph, were in fact catalysed by Cpd I mimics [47]. Their results shed light on the electrochemical parameters of Cpd II, but gave little hint as to the C–H bond activating ability of the employed oxidants.

Up to our knowledge, theoretical considerations of the dependence of reaction pathways, in particular selectivity and reactivity of Cpd II models with varying porphyrin substituents, are not known. The reason for this is probably two-fold. On the one hand, taking into account full porphyrin ligand, with all peripheral groups, would be too computationally demanding for current DFT applications, due to the size of the model. On the other hand, the reactivity studies are still mostly focused on Cpd I mimics, as the prominent reactive species. As already mentioned, catalysis by Cpd II gained new interest only within the last years. Within the short time limit, however, both obstacles will hopefully be overcome giving insight into the relationship between the porphyrin ligand structure and catalytic performance of model Cpd II systems, e.g. through application of hybrid QM/MM (quantum mechanics/molecular mechanics) methods.

4 Conclusions

It is believed that for a given substrate the performance of any catalyst may be improved by a proper choice of its composition and structure. In case of porphyrin-based systems, this may be achieved by changing the macrocycle ring substituents or the metal axial ligand.

Review of the literature data on the influence of the axial ligand on the structural parameters of the Cpd II mimic revealed that the stronger Fe-axial ligand bond, the weaker the Fe(IV)=O one. The source of this effect laid either in the trans effect or is due to the insertion of the iron ion in the porphyrin plane.

The mechanistic studies of the reactions catalysed by Cpd II mimics with varying axial ligands demonstrated that the type of axial ligand has only subtle, if any, effect on their reactivity.

More importantly, there is a pronounced impact of ligation as such on catalytic performance of the systems examined thus far. First of all, the two-state reactivity mechanism came into play in un-ligated systems and the change between triplet and quintet multiplicity surfaces were observed. What is more, the presence (or absence) of the axial ligand may switch the reactivity, if more than one reaction pathway is possible.

Incomplete data on the effect of porphyrin ring substituents exist, not allowing for the exhaustive description of the interplay between their presence and the type on the structure and activity of Cpd II models. One may learn, however, that the meso-substituents modify the Fe(IV)=O bond electronically, i.e. by influencing the donating properties of the pyrroline nitrogen atoms and sterically, i.e. disturbing the planarity of the central part of the complex.

In conclusion, we hope that future will bring more data which will supplement our rather limited knowledge about factors determining reactivity of the model Cpd II complexes. We believe that this may only be achieved by a synergy between theory and experiment, which enable more thorough, complementary studies of the reactivity parameters of high-valent iron-oxo species.

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