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Review

Non-innocent ligands in bioinorganic chemistry—An overview

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ABSTRACT

This review touches the most common instances where non-innocent ("suspect") behaviour of redox-active ligands, either substrates or supporting components, is observed in a biochemical context. These ligands include the $O_2/O_2^{\bullet-}/O_2^{2-}$, $NO^+/NO^{\bullet}/NO^-$, *o*-quinone/*o*-semiquinone/catecholate and tyrosyl/tyrosinate redox systems, the tetrapyrrole (porphyrinic) ligands, the pterins and flavins, and the dithiolene/ene-dithiolate ligands in molybdo- and tungstopterin. These non-innocent ligands are discussed in their interaction with biological iron, copper, manganese, molybdenum or tungsten centers.

1. Introduction: non-innocent ligand behaviour within the oxidation state concept

Although the oxidation state concept, so widely used in inorganic chemistry as illustrated by textbooks [1], is periodically criticized [2] because of its obvious limitations in certain areas such as organometallic chemistry, its usefulness in establishing "physical oxidation states" [3] is never seriously disputed. Among the consequences from this concept in the field of coordination chemistry is the occurrence of situations, in which the assignment of oxidation states is not *a priori* obvious, because the ligands can also undergo electron transfer and thus "ligand oxidation state" changes. Such ligands, e.g. $O_2/O_2^{\bullet-}/O_2^{2-}$ or $NO^+/NO^{\bullet}/NO^-$, were classified by Jørgensen [4] as "suspect" (or "non-innocent" or "guilty" [4]), in contrast to "innocent", unequivocally charge-defined ligands such as H_2O, NH_3 or Cl^- [5]. Based on experience in the usage of such wording, Ward and McCleverty have more precisely defined a *non-innocent behaviour* of "ambi-valent" ligands [6] because this response may depend on the metal partner. Since redox-active ligands changing their charge by just one elementary unit will necessarily form radical species, the increasingly recognized significance of radical ligands [7] in biochemistry [8–10] and elsewhere [11] has contributed to the renewed interest in the concept of "non-innocence" [12]. It goes without saying that there are many examples of non-innocently behaving ligands without any bioinorganic [13] relevance, Scheme 1 shows a few such redox-active metal-binding systems [14–16]. α-Diimines were among the earliest [17] but not always clearly recognized examples [18].

The alternative coordination situation between a redox-active transition metal $M^{y/y+1}$ and a non-innocent ligand $NIL^{x/x-1}$ can imply either a resonance situation (1) with delocalized valences in a single minimum or an equilibrium (2) between two

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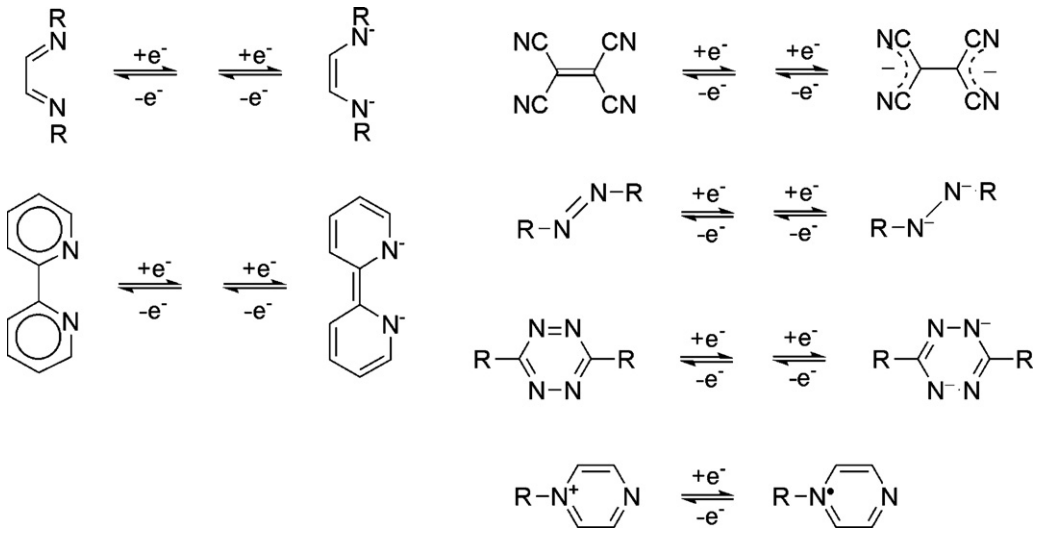


Scheme 1.

different "redox isomeric" or "valence tautomeric" species in a double minimum arrangement [19,20].

$$(NIL)^{x}M^{y}L_{n} \leftrightarrow (NIL)^{x-1}M^{y+1}L_{n} \quad \text{barrierless, } \rightarrow \text{ "resonance"} \quad (1)$$

$$(NIL)^{x}M^{y}L_{n} \rightleftharpoons (NIL)^{x-1}M^{y+1}L_{n}$$

$$\text{barrier, } \rightarrow \text{ "valence tautomerism"} \quad (2)$$

NIL = non-innocent ligand.

Electroactive and thus non-innocently behaving ligands occur not infrequently in bioinorganic chemistry [21], either as substrates (e.g. O_2, NO, quinones) or as supporting and therefore property-modifying redox-active cofactor ligands (porphyrins, quinones, dithiolate arrangements). This overview will also show that there are several documented cases where several different non-innocent ligands interact and cooperate synergistically with the redox-active metal ion (see Section 9).

2. The classical case of $O_2/O_2^{\bullet-}/O_2^{2-}$ as non-innocently behaving ligands

Dioxygen, superoxide (hyperoxide radical anion), and peroxide have long been recognized as part of a non-innocent ligand series [22]. The early established differences between the triplet neutral species O_2, the doublet intermediate $O_2^{\bullet-}$, and the diamagnetic but still only metastable O_2^{2-} could not prevent that a fierce and still ongoing debate [23,24] evolved on the proper description of the oxymyoglobin (and oxyhemoglobin) structure (Scheme 2).

(The formulae used in Scheme 2 and in the following are reduced to a minimum in order to focus on the interaction between the metal(s) and non-innocent ligand(s). The *innocent* co-ligands such as most amino acid residues from protein side chains or (in some instances) tetrapyrrole macrocycles are *not* drawn although they contribute to the electronic properties of the metal centers.)

$$Fe^{II} \text{ (high spin, } S = 2) \; + \; O_2 \text{ (high spin, } S = 1) \rightarrow$$

$$Fe^{II}(O_2^{0}) \text{ (both low spin; Pauling [23a])}$$

or

$$Fe^{III}(O_2^{\bullet-}) \text{ (both low spin and antiferromagnetically coupled; Weiss [23b])}$$

Scheme 2.

A recent overview describing this dispute and providing new calculation results [24] appears to show a preference for the Weiss formulation which would reveal the dioxygen ligand as behaving non-innocently, i.e. undergoing electron transfer in this reversible reaction.

The other oxygen transport proteins with non-heme containing dinuclear iron (hemerythrin [25]) or copper centers (hemocyanin [26]) exhibit a two-electron shift (3) between the differently coordinated [13] O_2/O_2^{2-} ligands and the dinuclear metal site.

$$O_2 + (M^{x})_2 \rightleftharpoons (O_2^{2-})(M^{x+1})_2 \quad (3)$$

M^{x} = Fe^{II} or Cu^{I}.

While the $Fe^{III}(O_2^{\bullet-})$ alternative is also discussed for intermediates in catalytic cycles of P450 monooxygenases [13,27], a further ambivalence between superoxo [28] and peroxo ligands can be assumed for partially reduced reactive species $Fe^{III}(O_2^{2-})/Fe^{II}(O_2^{\bullet-})$ in such cycles.

The dioxygen non-innocent ligand system is distinguished by its capability to function beyond the $(O_2)^{n}$ states (n = 0, 1−, 2−) in a biochemical context. Three- and four-electron reduction of O_2 via O_2^{2-} by an oxidizable metal results in O–O bond cleavage to produce oxyl/hydroxyl ($O^{\bullet-}/{}^{\bullet}OH$) radicals or oxide ions. The former is known as Fenton chemistry [29], mostly formulated as

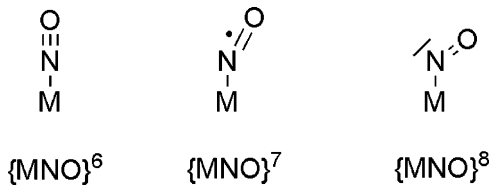
$$M^{n} + H_2O_2 \rightarrow M^{n+1}(OH) + {}^{\bullet}OH \quad (4)$$

M = Fe and n = +II, or Cu and n = +I while the latter may be represented by the alternative (5) for dicopper/dioxygen interaction [30].

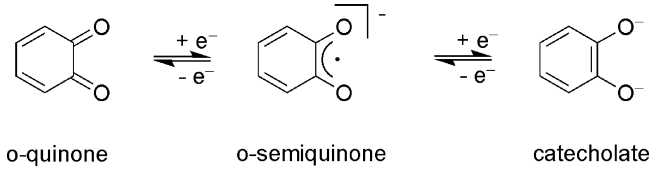
$$2Cu^{I} + O_2 \rightarrow Cu^{II}(\mu\text{-}O_2)Cu^{II} \rightarrow Cu^{III}(\mu\text{-}O)_2Cu^{III} \quad (5)$$

3. The $NO^{+}/NO^{\bullet}/NO^{-}$ ligand system: a late addition to biorelevant non-innocent ligands

The seminal discovery [31] of the extensive role of NO in biochemical information transfer [32] has revived a part of coordination chemistry [33] that was fascinating but lay dormant for some time. Immediately, the non-innocent ligand potential of the system nitrosyl cation/nitric oxide radical/nitroxide anion [33,34] was remembered and assumed to be a crucial factor for the *in vivo* activity of "NO" [32]. In fact, Jørgensen had identified NO as "the simplest case of a suspect ligand" [4]. In the course of more recent investiga-



Scheme 3.



Scheme 4.

tions there was also a reappraisal of classical but never questioned assignments (e.g. of the brown ring species in the classical nitrate test as $Fe^{III}(NO^-)$ and not as $Fe^{I}(NO^+)$ [35]) and a reinvestigation of well known species such as the nitroprusside ion $[Fe(CN)_5(NO)]^{2-}$ by more contemporary methodology [28,36,37].

The increasingly available structural information also proved advantageous in the analysis of bonding with non-innocent NO because the binding of the very strong π electron acceptor NO^+, the neutral radical $NO^•$, or the strong electron donor NO^- could be differentiated on the basis of the M–N–O angle within the electron pair repulsion model (Scheme 3) [34].

In addition, the established Enemark–Feltham notation $\{MNO\}^x$ [34] (Scheme 3) could be used which deliberately neglected to assign oxidation states individually to the metal or to NO^n but assumed a large degree of covalent bonding. Such concepts were confirmed later, e.g. through unexpected invariant spin distribution in $L_nRu(NO)$ complexes with $\{RuNO\}^7$ configuration, regardless of the ancillary ligands L_n [38].

An important question discussed mostly for heme (Fe-porphyrin) species involves the alternative (6) between the formulations

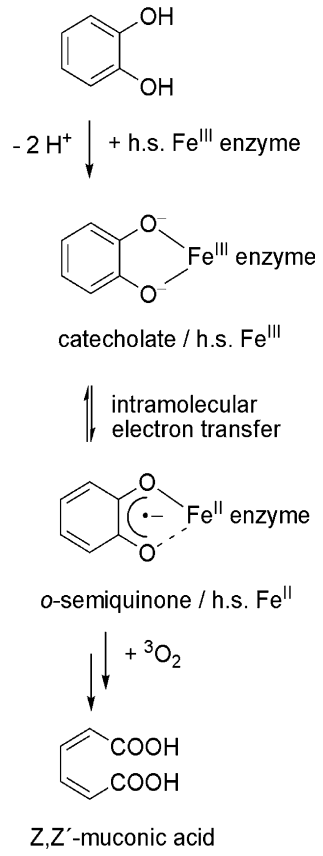
$$Fe^{II}(NO^+) \text{ or } Fe^{III}(NO^•) \quad (6)$$

Detailed experimental and computational studies by Lenhert and coworkers have shown that rather small energy differences may occur between the two alternatives [39] which are further influenced by the potential of porphyrin non-innocence and of spin crossover.

One-electron reduction would lead to the alternatives in (7)

$$Fe^{I}(NO^+),\ Fe^{II}(NO^•) \text{ or } Fe^{III}(NO^-) \quad (7)$$

for the $\{FeNO\}^7$ configuration which have already been mentioned in connection with the brown ring reaction [35]. The complication from various accessible spin states clearly adds a further dimension here to the non-innocent ligand ambivalence, however, techniques such as Mössbauer and EPR spectroscopy for paramagnetic species allow to identify $[Fe^{III}(H_2O)_5(NO^-)]^{2+}$ [35] and $[Fe^{II}(CN)_5(NO^•)]^{3-}$ [37].



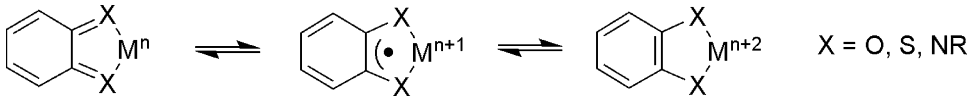
Scheme 6.

4. Biochemical roles of the 1,2-dioxolenes as the prototypical organic non-innocent ligands (*o*-quinone/*o*-semiquinone/catecholate)

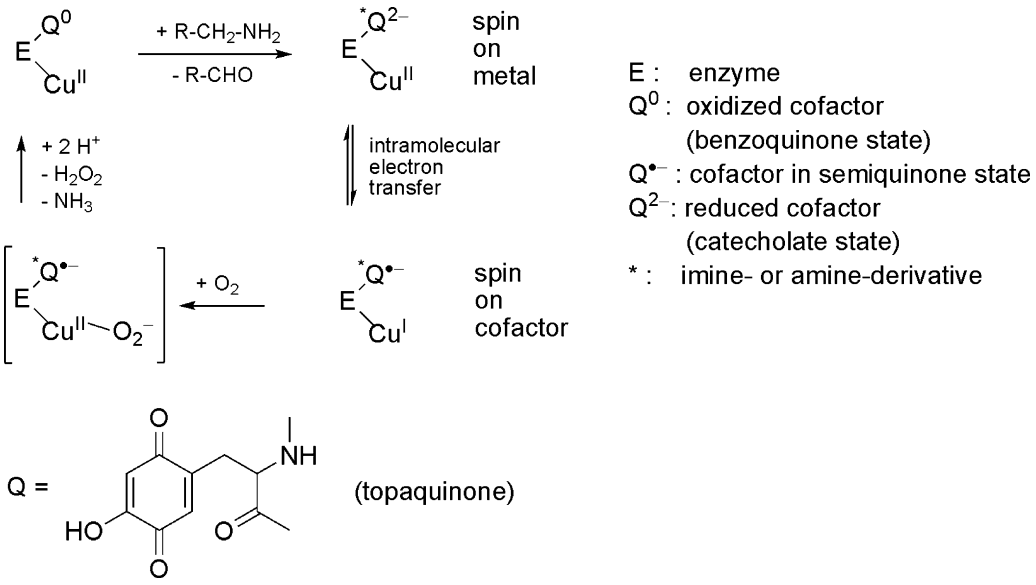
Probably the most researched non-innocent organic ligands are those derived from the catecholate/*o*-quinone redox system, with the *o*-semiquinone as the frequently persistent intermediate form. The non-innocent behaviour of these excellent chelate systems (five-membered ring formation) has been recognized, formulated and reviewed rather early [40,41], and unusual phenomena such as delocalized bonding [42,43] or valence tautomerism [19,20] were described for these ligands in their ring substituted and O/NR exchanged forms (see Schemes 4 and 5).

Biological relevance for quinones (*o*- and *p*-isomers [44]) is obvious, given their ubiquitous role in photosynthesis [45] and respiration [46], in many enzymatic processes [47], and in their nutritional (antioxidants, vitamins [48]), pharmaceutical [49], pathogenic (carcinogenesis, Parkinson's disease) and toxicological functions [50]. Specific non-innocent behaviour has been discussed for iron and copper proteins: Catechol dioxygenases specializing in intra-diol cleavage (see Scheme 6) contain single non-heme iron centers which are assumed [51] to be chelated by the catecholate substrates and undergo an intramolecular electron exchange process (8)

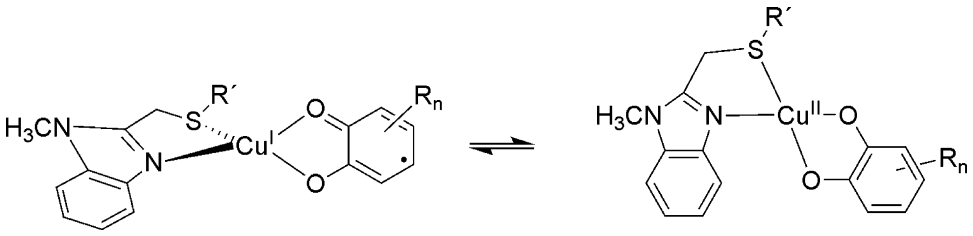
$$\text{iron(III)/catecholate} \rightarrow \text{iron(II)/semiquinone} \quad (8)$$



Scheme 5.



Scheme 7.



Scheme 8.

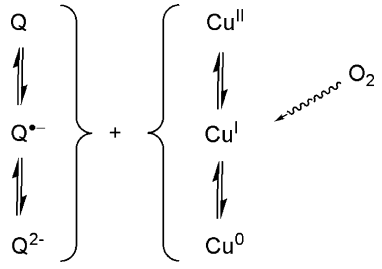
which allows the binding and reductive activation of the other substrate molecule, $^3O_2$.

In a similar way, Cu-dependent amine oxidases [52] contain a single metal ion Cu^{2+} per subunit which may interact with substrate-reduced multifunctional "topaquinone" (TPQ, Scheme 7), i.e. an electron-rich aromatic compound, to produce EPR-detectable semiquinone [53] and a copper(I) center ready for O_2 binding and activation. Such intramolecular electron-exchange equilibria

$$\text{copper(II)/catecholate} \rightleftharpoons \text{copper(I)/}o\text{-semiquinone} \quad (9)$$

could be reproduced spectroscopically in model systems (Scheme 8) [54].

Comparable redox potentials of $Cu^{0/I/II}$ and $Q^{0/-I/-II}$ (Scheme 9) are thus relevant in combination not only for materials science (ferromagnetically coupled Cu^{II}–$Q^{\bullet-}$) and organic synthesis ("copper catalysis") but also in biochemistry for the biosynthesis of neurotransmitters such as catecholamines, the biosynthesis of pigments like melanin, the biosynthesis of cofactors (e.g. tyrosine → topaquinone), for enzymatic oxidation (amine oxidases), lignin degradation (catechol enhanced Fenton reaction) and antioxidant activity such as radical scavenging.



Scheme 9.

While the less reduced quinones do not typically form inert coordinative bonds they may still be expected, as non-innocent ligands, to be involved in further electron transfer activity versus transition metals in biochemistry. *o*-Quinones provide a natural chelating binding site (see Schemes 4 and 5) whereas *p*-quinones may have to use additional donors for chelation [44,55].

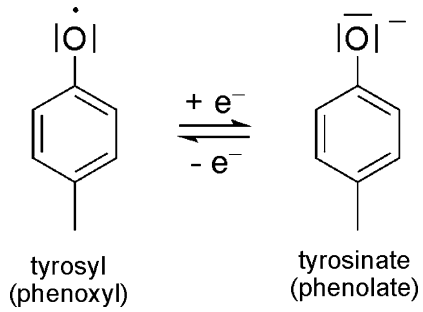
5. Cooperation of the tyrosyl/tyrosinate redox pair with iron, copper or manganese in metalloenzymes

The binding of deprotonated tyrosine to high-valent metals, especially iron(III), has long been known as a source of intense absorption in the visible region, leading to colouring of proteins such as transferrin or purple acid phosphatases [56]. The formulation of this process (10) already points to the potential of such a combination for electron transfer in the ground state, leading to complexes of the neutral, oxidizing tyrosyl radical (Scheme 10).

$$Fe^{III}/Tyr^- \xrightarrow[LMCT]{h\nu} [Fe^{II}/Tyr^{\bullet}]^* \quad (10)$$

In fact, electron exchange and the magnetic interaction of the tyrosyl radical with iron, copper and manganese has been established in important proteins such as ribonucleotide reductase (Fe [57]), galactose oxidase (Cu [58]), and in photosystem II of photosynthesis (Mn [59]).

Whereas the oxidative power generated from the $(Fe\cdots Fe)/O_2$ interaction in ribonucleotide reductase serves to convert tyrosinate to tyrosyl on the way to radical involving ribonucleotide deoxy-



Scheme 10.

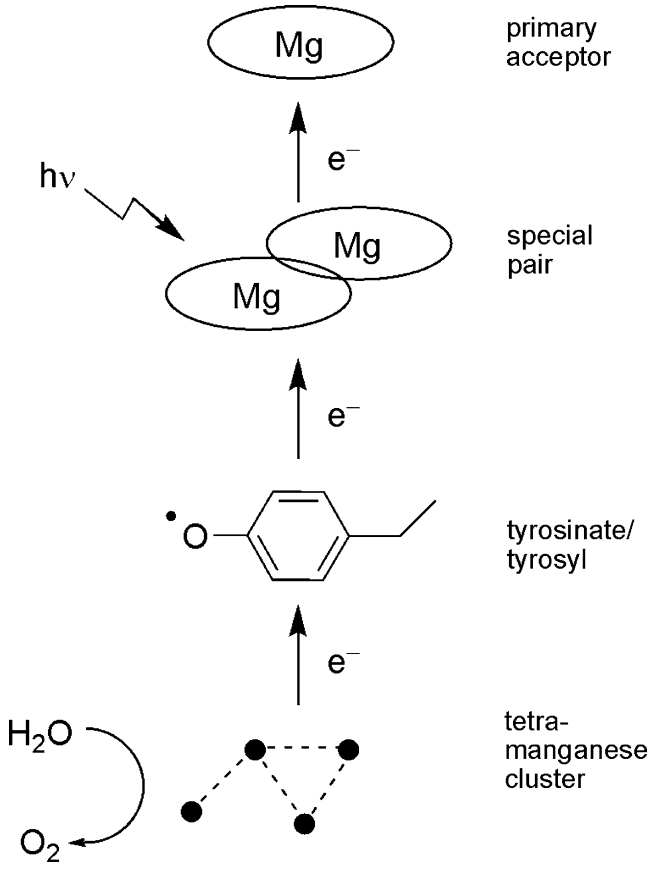
genation [57,60], the coordination of one cysteinyl-substituted, i.e. electron-rich tyrosinate to copper allows for a combined Cu(II)/tyrosyl action to oxidize primary alcohols to aldehydes (Scheme 11 [58]).

The essential tyrosine/tyrosyl redox pair in photosystem II mediates the electron flow (Scheme 12) from the catalytic $CaMn_4$ metal cluster site of water oxidation to the photoexcited special pair at the center of the photosystem [59].

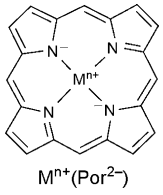
It is interesting to witness the recent surge [8,9,60] in biochemical radical chemistry which mostly involves metal activation of non-innocent organic functions.

6. Essential non-innocence of tetrapyrrole (porphyrinic) ligands in biochemistry

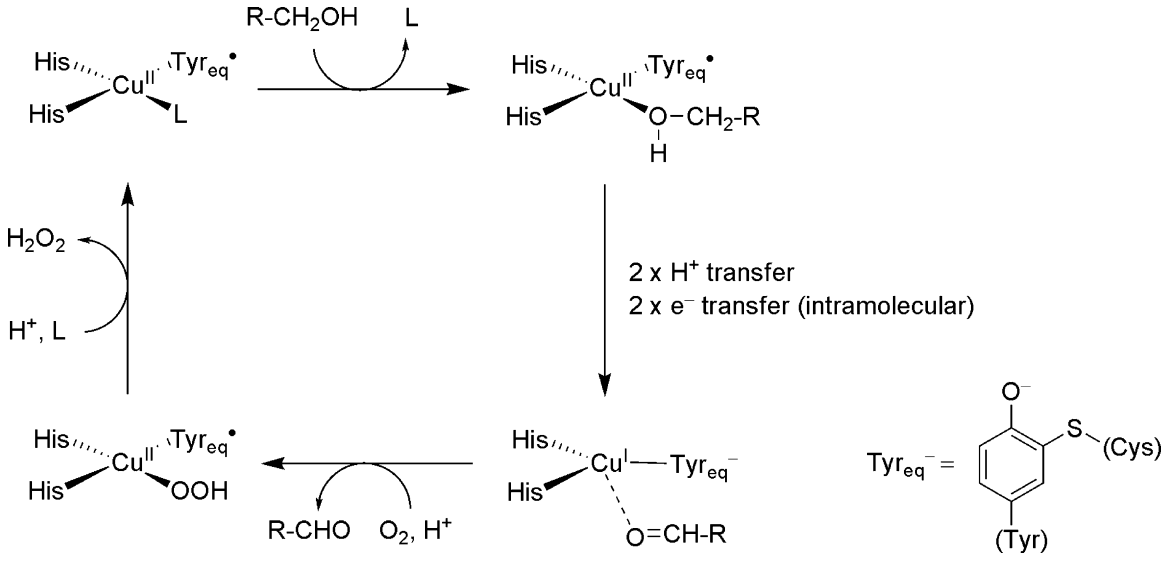
The excellent chelating coordination properties of macrocyclic tetrapyrrole ligands such as the porphyrins [61] have sometimes masked their great potential for non-innocent behaviour *in both directions*, i.e. towards oxidation and reduction. As the standard form of porphyrins is that of a dianionic tetradentate macrocycle (Por^{2-}), the one-electron oxidized forms involve the radical anion $Por^{\bullet -}$ whereas the one-electron reduced state corresponds to a radical trianion $Por^{\bullet 3-}$ (Scheme 13). While such redox states (and beyond) of porphyrins and related ligands in their metal complexes (e.g. metalloporphyrins) can be conveniently generated electrochemically or via suitable chemical processes [62], their occurrence is more limited but nonetheless well documented in bioinorganic chemistry.



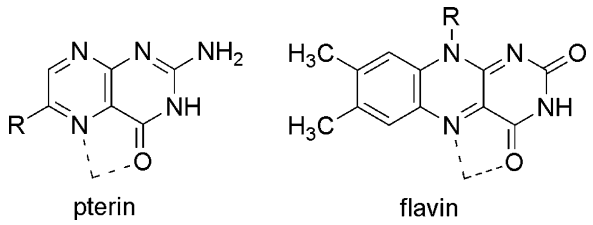
Scheme 12.



Scheme 13.



Scheme 11.



Scheme 14.

One most important intermediates involves the highly oxidized states in catalytic cycles of P-450 monooxygenation ("compound I" [27,28,63a]) and peroxidase action ("HRP I" [63b]). In both instances, the interaction with $O_2 + e^- + e^-$ (P-450) or H_2O_2 (peroxidases) on heme-iron(II) results in an oxidized reactive species (11a) and (11b) which may be best described [13,27,28,63] by an oxo-ferryl(IV) center $[Fe{=}O]^{2+}$ coordinated to a one-electron oxidized porphinato ligand:

$$\{(Por^{2-})Fe^{III}\}^{+} + O_2 + 2e^- + 2H^+ \rightarrow H_2O + \{(Por^{\bullet -})([Fe^{IV}O])\}^{\bullet +} \quad (11a)$$

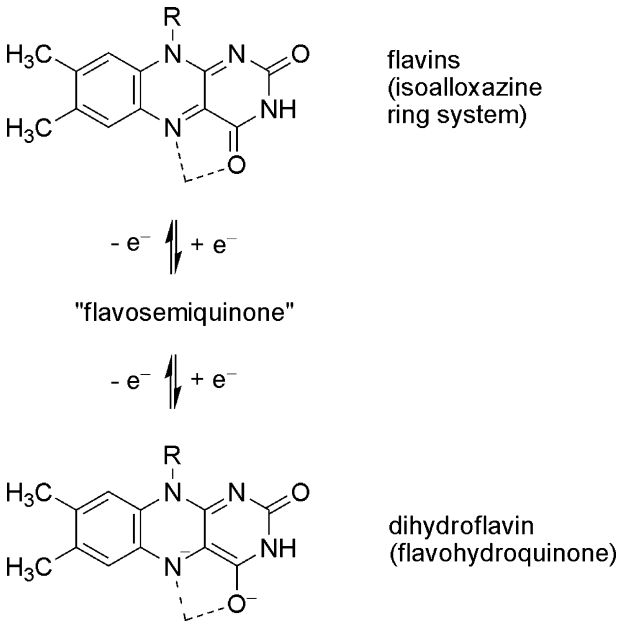
$$\{(Por^{2-})Fe^{III}\}^{+} + H_2O_2 \rightarrow H_2O + \{(Por^{\bullet -})([Fe^{IV}O])\}^{\bullet +} \quad (11b)$$

Although they contain a porphinato radical anion ligand (11a) and (11b), such species are usually referred to as "radical cations" [63a], they have been studied at low temperatures and have characteristical absorption [27,63].

In contrast, the magnesium(II) complexes of certain chlorins known as chlorophylls can serve as primary electron acceptors in photosystem I of photosynthesis whereby the photoproduced electron from charge separation within the "special pair" is added by the macrocyclic π system to convert it from a dianion to a paramagnetic, EPR-detectable trianion [64a].

$$(Chl^{2-})Mg^{2+} + e^- \rightarrow (Chl^{\bullet 3-})Mg^{2+} \quad (12)$$

Although the lifetime of this intermediate is only in the order of a few picoseconds in the photosynthetic process [64], its occurrence is crucial for the (irreversible) separation of charges within the photosynthetic membrane.



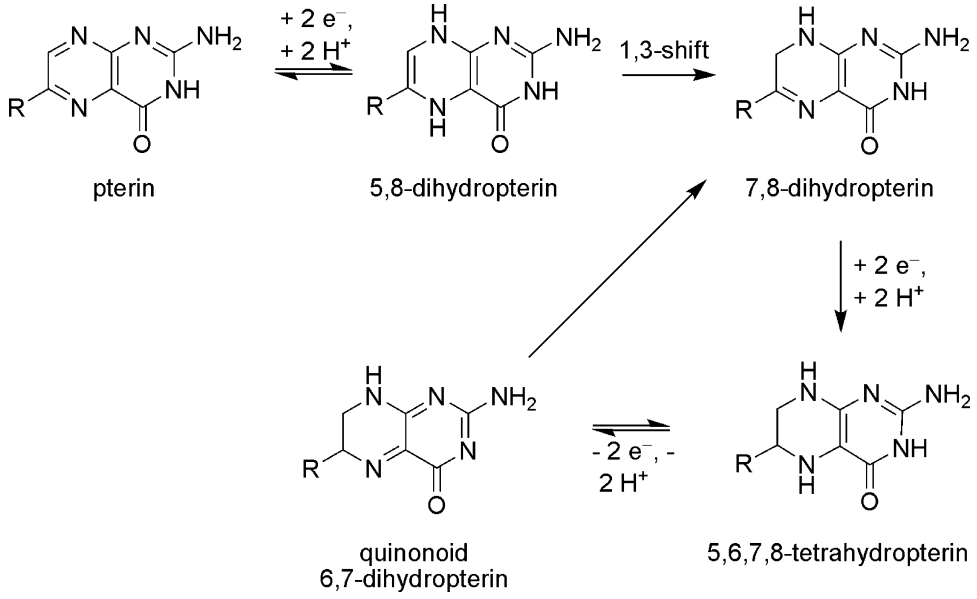
Scheme 15.

7. Potential for non-innocent ligation by pterins and flavins

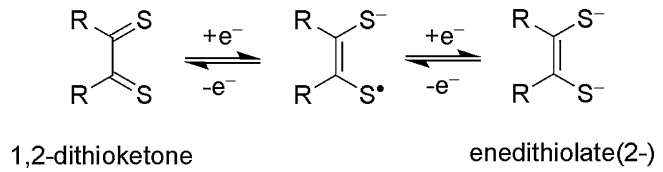
Pterins and flavins are redox-active cofactors in their own right [65,66] which can even function as O_2 activating species in enzymes without direct support by metal centers [66,67].

Their complex heteroatom-rich π systems do not only allow for multiple H-bonding and a π/π interaction potential, they also facilitate multiple reversible electron transfer and permit metal coordination, preferentially at the O4-N5 chelating site [68] (see Scheme 14).

The intrinsic redox reactivity of flavins involves two frequently separated one-electron transfer steps with an aromatic oxidized form, a flavosemiquinone intermediate, and a formally antiaromatic (8 π electron) "flavohydroquinone" state [66,69] (Scheme 15).



Scheme 16.



Scheme 17.

Biochemically useful switching between sequential 1e transfers and one 2e transfer appears to be possible by environmental control, including structural effects [66,69].

The pterin redox system [65,70] is different because it involves a tetrahydro state and several dihydro species (Scheme 16) while odd-electron intermediates seem to be less important.

The proven enhancement [68,71,72] of redox reactivity of pterins and flavins after metal ion binding has initiated speculation on such mechanisms in biochemical processes. However, electron exchange between metal functions and flavin or pterin cofactors in enzymes does not usually require direct coordination, it can make use of the suitability of proteins for electron transfer mediation.

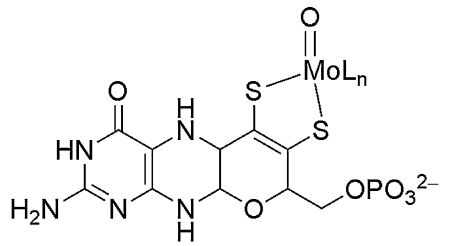
A special case, however, is the dithiolene containing pyranopterin system (Scheme 19 [70,73]) which combines pterin redox chemistry, pyran ring opening potential, and the specific non-innocent ligand potential of the dithiolene/ene-dithiolate function (Scheme 17).

8. Non-innocent dithiolene/ene-dithiolate ligands in molybdo- and tungstopterin

As outlined in detail in this volume, the dithiolenes constitute a prototypical class of non-innocently behaving ligands, especially towards "soft" transition metal centers [4,74]. Similarly as in diimino-*o*-quinone compounds of ruthenium [43,75], these species exhibit a high degree of covalent bonding with extensively delocalized electrons and corresponding difficulties to apply conventional oxidation state nomenclature.

Formally, however, the α-dithiolenes fit right into the general scheme (Scheme 18) of chelating non-innocent ligands.

The biochemically active molybdopterin or tungstopterin (Scheme 19) structures include a substrate binding Mo or W center with oxo and/or other donor ligands, bound in a classical fashion to one or two ene-dithiolate chelates the back of which is connected to the pyran ring of a tricyclic "pyranopterin" heterocycle [73,76].



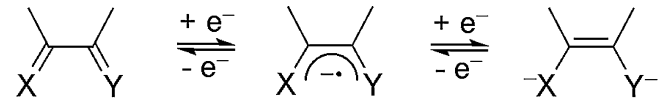
M = Mo: molybdopterin, Mo-cofactor ("Moco") of oxotransferases (pyranopterin ligand);
M = W: tungstopterin

Scheme 19.

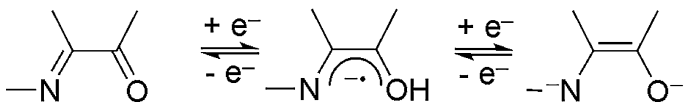
combination non-innocent ligand/metal	representative examples
Por / Fe / O_2 or NO	*Mb*, *Hb*, P450, NOS
Tyr / Fe_2 / O_2	ribonucleotide reductase
Q / Fe / O_2	catechol dioxygenase
Q / Cu / O_2	amine oxidase
Tyr / Cu / O_2	galactose oxidase
tetrahydropterin / dithiolene / MoO	molybdopterin

Scheme 20.

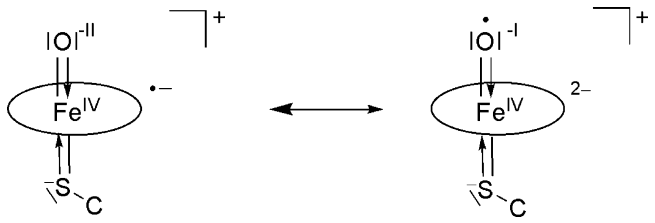
While the function potential of pterins is obvious (Scheme 16) and the dithiolene/ene-dithiolate non-innocent ligand interacting with M^{IV} to M^{VI} species is well understood [77], there is a discussion how the facile pyran ring opening can affect the pterin oxidation state and allow the pterin redox system to interact with the substrate-converting metal-dithiolene center during the enzymatic process [70].



X, Y = O : α-dicarbonyl compounds, incl. o-quinones, *o*-semiquinones, catecholates
X, Y = S : α-dithiolenes
X, Y = NR : α-diimines
X = O, Y = NR : α-iminocarbonyl compounds



Scheme 18.



Scheme 21.

9. Summary and perspective

Apart from the more obvious advantages from non-innocence, e.g. lowered reorganization energy for electron transfer through delocalization or spin crossover, the cooperation [21] between two different non-innocent ligands occurs in several bioinorganic configurations (Scheme 20) with the benefit of multifunctionality such as separated but communicating electron transfer and reaction centers.

Functional modeling of such combinations is also possible, e.g. by assembling NO together with porphyrin or quinonoid ligands at redox-active ruthenium [78].

While this rather brief overview has focussed on the more obvious instances of non-innocent ligand behaviour in bioinorganic chemistry, there may be hidden such situations which could involve, e.g. cysteinato ligands, Cys^-, acting more as cysteinyl radicals, $Cys^{\bullet}$: $(Cys^-)M^n/(Cys^{\bullet})M^{n-1}$. Even the humble oxide, O^{2-}, may thus acquire significant oxyl ($O^{\bullet-}$) character, as assumed for the highly oxidized intermediates (13) of oxoferryl-heme containing P-450 systems:

$$[Fe^{IV}(O^{2-})(Por^{2-})] - e^- \rightarrow [Fe^{IV}(O^{\bullet-})(Por^{2-})]^+$$
$$\text{or } [Fe^{IV}(O^{2-})(Por^{\bullet-})]^+ \text{ or } [Fe^{V}(O^{2-})(Por^{2-})]^+ \quad (13)$$

Axial ligation by σ and π electron-rich cysteinate (Scheme 21), another potentially suspect ligand as indicated above, seems to favour the first alternative which then causes the H abstraction/OH rebound sequence assumed for the P-450 productive mechanism [27,63a].

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