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Coordination compounds of pteridine, alloxazine and flavin ligands: structures and properties

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Contents

Abstract

The pteridine and (iso)alloxazine π systems are the underlying heterocyclic structures of coenzymatic constituents (pterins, lumazines, flavins) of oxidoreductase enzymes. These molecules are potential ligands for metal centers which, in the absence of additional coordination sites, bind predominantly through O(4) and N(5) to form five-membered, redox-active α-iminoketo chelate rings. Recent results from spectroscopic and electrochemical studies and structural data are summarized in this article.

Keywords: Chelate coordination; Coenzymes; Flavins; Pteridines; Structures

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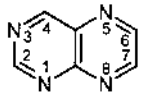
1. Introduction and scope

The coordination chemistry of biomolecules has largely focused on proteins, involving the side chain functions of amino acids [1]. More recently, nucleic acids and their constituents (such as the nucleobases) and carbohydrates have attracted increasing attention [1–3]. Of the smaller bioligands, the tetrapyrrole and non-conjugated macrocycles (ionophores) continue to be intensely researched [1,4,5]. Small coenzymes, on the other hand, have received less recognition as ligands for metal centers; most work in this area has centered on ascorbate [6,7]. In the 1970s there was some consideration given to the chemistry and possible biological role of flavin–metal interactions [7–21]; later work has concentrated more on the related pterin systems [22–34] in connection with the long unresolved question of pterin–metal interactions in oxo-transferring molybdoenzymes [1,35] and other metal- and pterin-dependent oxidases [1,36].

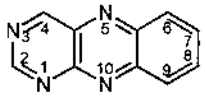
Complementing a current report on the electron transfer reactivity in transition metal/pteridine complexes [37] we wish to review in this article recent work on the electrochemistry, spectroscopy and structure of metal complexes with flavin- and pterin-type ligands. A comprehensive list of structural data is provided.

2. Nomenclature and brief description of the biochemical functions

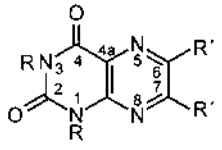
The underlying heterocyclic structures of the pterin and flavin biomolecules are 1,3,5,8-tetraazanaphthalene (pteridine) **1** and 1,3,5,8-tetraazaanthracene (benzo[*g*]pteridine) **2**. The 2,4-dioxo derivatives are referred to as lumazines **3** and alloxazines **4**; the biochemically most important systems such as biopterin **5e**, folic acid **5f** or riboflavin (vitamin B_2, **6c**) are derived from pterin (2-amino-4-oxo-(*3H*)pteridine, **5a**) or isoalloxazine **6a**, respectively (flavin = 7,8-dimethyl-isoalloxazine).



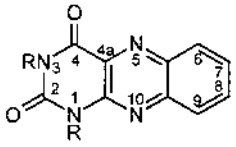
1 pteridine



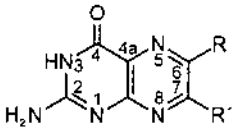
2 benzo[*g*]pteridine



3a R = H, R′ = H
lumazine,
3b R = Me, R′ = H
1,3-dimethyllumazine
3c R = R′ = Me
1,3,6,7-tetramethyllumazine

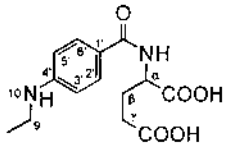


4a R = H
alloxazine
4b R = Me
1,3-dimethylalloxazine



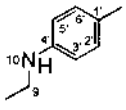
5a R = R′ = H — pterin
5b R = Me, R′ = H — 6-methylpterin
5c R = R′ = Me — 6,7-dimethylpterin
5d R = COO⁻, R′ = H — pterin-6-carboxylate
5e R = CH(OH)CH(OH)CH_3, R′ = H — biopterin

5f R =

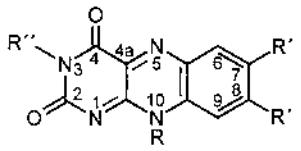


R′ = H — folic acid

5g R =

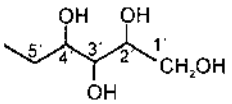


R′ = H — 6-[N-(p-tolyl)-aminomethyl]-2-pivaloylpterin



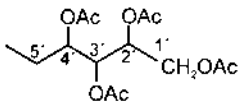
6a R = R′ = R″ = H — isoalloxazine
6b R = Me, R′ = R″ = H — 10-methylisoalloxazine

6c R =



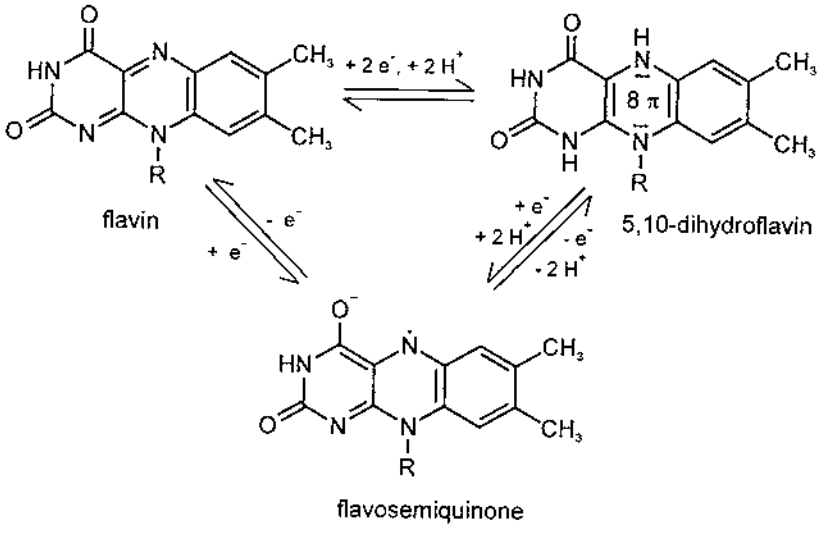
R′ = Me, R″ = H — riboflavin

6d R =



Ac = $(CO)CH_3$, R′ = Me, R″ = Et — 1′,2′,3′,4′-tetraacetyl-3-ethyl-riboflavin

The flavins are essential constituents of ubiquituous electron transfer proteins ('flavodoxins') and oxidoreductases ('flavoenzymes') [8,38]. The most relevant substituted form is riboflavin **6c** from which flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) are derived. The flavins usually undergo a stepwise one-electron reduction via the paramagnetic 'flavosemiquinone' radical to the Hückel-'antiaromatic' flavohydroquinone state with eight conjugated π electrons in the central pyrazine ring [7,39,40] (Scheme 1).

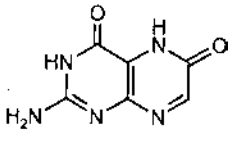


Scheme 1.

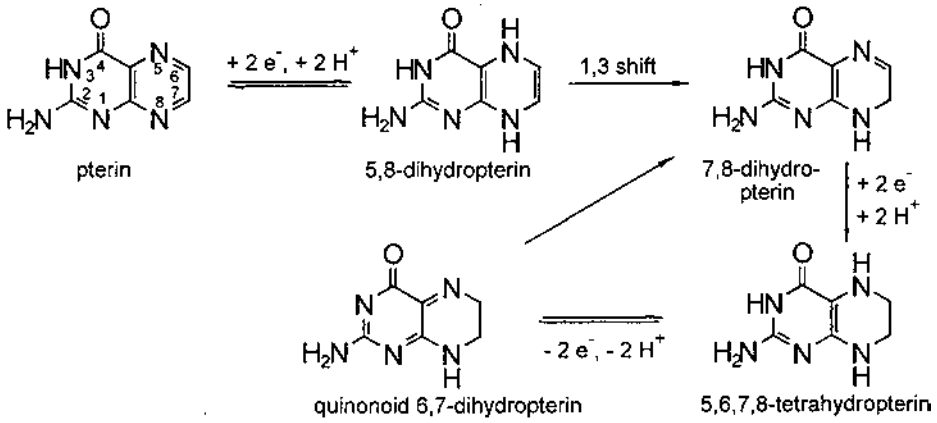
The remarkable features of the flavoenzymes include their capability to act either as two-electron or as two-fold one-electron reagents ('redox switching') and, in the dihydroflavin form, to activate oxygen O_2 in its triplet ground state in the absence of metal centers [8,38]. The low-lying π^* orbital of this heterocyclic system with a large orbital coefficient at the 4a position are thought to be responsible for this unusual function; geometric flexibility in the reduced state also seems to play a role [8,38,41].

Although flavins have for some time been known to interact in vitro with metal ions in the aromatic and semireduced states (see Section 3) [7–21], their direct association (i.e. coordination) with metal species in vivo is not established [11].

The pterins are equally ubiquituous and essential coenzymes which occur primarily as the 5,6,7,8-tetrahydro forms of e.g. biopterin **5e**, folic acid **5f**, xanthopterin **7** or methanopterin [1] in metabolic cycles involving C_1 transfer and conversion or NO biosynthesis [42–45].



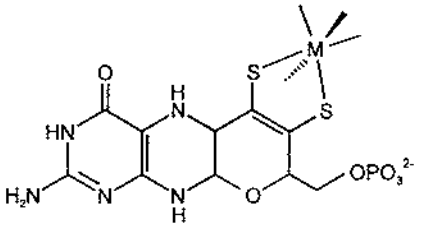
7 xanthopterin



Scheme 2.

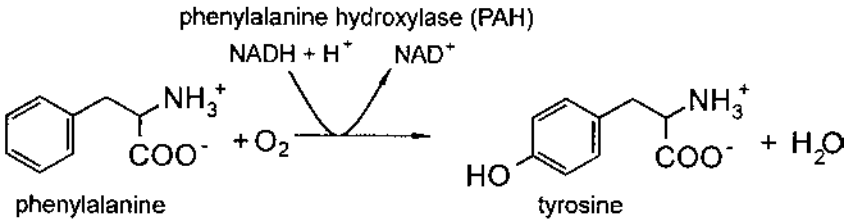
In the absence of an anellated benzo ring the redox-active pterin molecules do not form persistent one-electron reduced semiquinone (radical) or two-electron reduced eight π electron states under physiological conditions [39,46]. Instead, they exhibit rearrangement reactions (5,8 → 7,8 dihydro form) and further reduction to the biochemically most relevant tetrahydro species; the latter can be reoxidized to a third kind of dihydro state, the quinonoid form [1,39,43,44,46,47] (Scheme 2).

In context with metal coordination the most researched pterin derivative has been 'molybdopterin' (or 'tungstopterin') [35] which serves as active group in the Mo- or W-dependent oxotransferase enzymes (such as aldehyde or xanthine oxidase [48,49]) of various organisms, including thermophilic and hyperthermophilic species [35,50]. Recent protein crystallographic analyses have identified this pterin derivative as a tricyclic 'pyranopterin' structure **8** which contains a tetrahydropterin entity and a special metal binding ene-dithiolate ('dithiolene') function in the fused pyrane ring [35,51–53].



8 pyranopterin (metal coordinated)
M = Mo: "molybdopterin", M = W: "tungstopterin"
(tetrahydro form)

These particular pterin ligands seem to activate molybdenum or tungsten in the transfer of oxygen atom equivalents, i.e. in an enzymatic two-electron process [35].

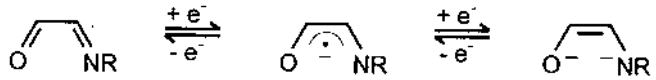


Scheme 3.

Other pterins such as tetrahydrobiopterin occur together with distant metal centers such as iron in enzymes like tyrosine hydroxylase or phenylalanine hydroxylase (PAH) which are essential for amino acid biosynthesis [36,54] (Scheme 3). The possible cooperation between the redox-active pterins and transition metals such as iron is still uncertain; metal-depleted forms are also capable of activating dioxygen which suggests a similar O_2-binding role for reduced pterins as for dihydroflavins [54]. While not directly coordinating to the catalytic heme iron, the tetrahydrobiopterin of NO synthase oxygenase dimer seems to influence the heme-bound O_2 molecule [42].

Compared to pterins and flavins the lumazines are of less importance in biochemistry although they may be found as natural products [55].

All three kinds of ligands, (iso)alloxazines, pterins and lumazines, contain the α-iminoketo function [56,57] as part of the heterocyclic structure. This unsaturated function is an asymmetric variety (X = O, Y = NR) of the redox-active chelate arrangement (Scheme 4) which is widely used in coordination chemistry, the most familiar symmetrical forms containing X,Y = NR (α-diimines [58,59]), O (α-diketones), and S (dithiolenes [60]).



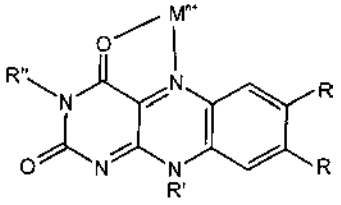
Scheme 4.

Due to the more straightforward redox and coordination behavior of the tricyclic heterocycles we first review the coordination chemistry of alloxazines, isoalloxazines and related species.

3. Complexes of tricyclic ligands (alloxazines, isoalloxazines, flavins)

Work summarized already in 1973 by Hemmerich and Lauterwein [9] and later by Clarke in 1984 [7] has shown that metal centers such as Cu^+, Ag^+, Cu^{2+}, Zn^{2+} or Ru^{2+} can bind to flavins or isoalloxazines in the N(5)–C(4a)–C(4)–O(4) chelate site which leads to the formation of largely planar five-membered chelate rings (see Section 5). Remarkably, there appeared to be a preference of non-reduced, i.e. π

electron-deficient flavins and isoalloxazines for 'soft', electron-rich centers such as Ru^{2+} or Cu^{+} whereas 'normal' electrophilic metal ions such as Zn^{2+} preferred coordination of the one-electron reduced semiquinone state (see Scheme 1) [7,9,10].



The biological electron transfer function of the flavins and their capability to exhibit (photo)catalytic effects in vitro has prompted a number of studies on the electrochemistry and charge transfer behavior of corresponding metal complexes. Clarke and coworkers have thoroughly studied electrochemical and other effects of tetraammineruthenium coordination to flavins in protic media [7,20,21,61,62]. As well known 'reporter groups' in complexes with π acceptor chelate ligands [58,63] the $[(bpy)_2Ru]^{2+}$ [64] and $Cl(CO)_3Re$ groups were later employed with riboflavin [56,65,66] to study electrochemical and metal-to-ligand charge transfer (MLCT) phenomena such as possible luminescence or solvatochromism [66]. Electron transfer reactivity of riboflavin and the corresponding flavosemiquinone towards metal-centered redox agents was studied mechanistically by kinetic methods [67].

The success with using 1,3-dimethylated lumazines in coordination chemistry [56,68–73] has recently prompted us to study complexes of 1,3-dimethylalloxazine **4b** [74,75]. Compounds $[(\mathbf{4b})Cu(PPh_3)_2](BF_4)$, $[(\mathbf{4b})Ru(bpy)_2](PF_6)_2$, $[(\mathbf{4b})Re(CO)_3Cl]$, $[(\mathbf{4b})IrCl(C_5Me_5)](BF_4)$ and $[(\mathbf{4b})WO_2Cl_2]$ were prepared, and the structural characterization of the latter two species confirmed the familiar O(4)/N(5) coordination mode (see Table 2) which was also assumed for flavin complexes of Mo^{IV} and Mo^{V} [76].

Similarly, as some metal compounds of flavins and isoalloxazines [7], the 1,3-dimethylalloxazine complexes showed reversible reduction to radical species (see Table 1 and Fig. 1). This reversibility allowed us to study the spin distribution by EPR (Fig. 2) and the change in light absorption on reduction (spectroelectrochemistry). Unexpectedly, the chlorine substituent was found to remain bound on Ir in $[(\mathbf{4b})IrCl(C_5Me_5)]^{\bullet}$ [74]. This observation and the EPR analysis suggest a low lying π^* orbital for spin accommodation but relatively little charge transfer from the reduced ligand $\mathbf{4b}^{\bullet -}$ to the organometallic fragment [69,74].

Considering the versatile and potent biological functions of flavins [37,38] there have been several efforts to utilize modified analogues such as **9a**–**c** to effect facilitated radical formation [77] and (photo)catalyzed oxidation [78–80] or reduction [81] of organic substrates through improved metal-heterocycle binding [82]. A ruthenium(III) complex $Ru(\mathbf{9d})_2(PPh_3)_2Cl$ containing the flavin-related phenoxazinylate ligand **9d** was structurally characterized to reveal the familiar O(4)/N(5)

Table 1
Reduction peak potentials[a,b] of related lumazine, alloxazine and pterin ligands and complexes

	L		
	3b [57,74]	**4b** [69,74]	**10b** [74]
Ligand L	−1.98	−1.68 (rev)	−1.83
$[(L)Ru(bpy)_2](PF_6)_2$	−1.04[c]	−0.82 (rev)[d]	−0.99[e]
$[(L)IrCl(C_5Me_5)](PF_6)$	−1.05 (rev)	−0.78 (rev)	−1.61[f]

[a] Cathodic peak potentials in V versus ferrocene/ferrocenium from cyclic voltammetry at 100 mV s^{-1}; electrochemically reversible processes denoted by (rev).

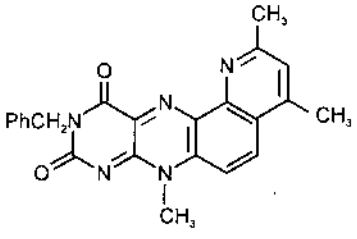
[b] In THF/0.1 M Bu_4NPF_6, except where indicated.

[c] In 1,2-dichloroethane/0.1 M Bu_4NClO_4.

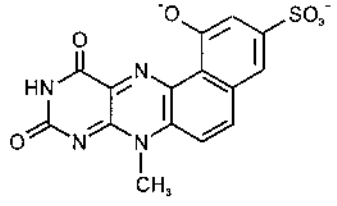
[d] Additional reversible one-electron processes at −1.70, −2.16 and −2.52 V; the latter two involve the stepwise reduction of coordinated 2,2′-bipyridine (bpy). Reversible, metal-centered oxidation occurs at 0.98 V.

[e] In acetonitrile/0.1 M Bu_4NPF_6.

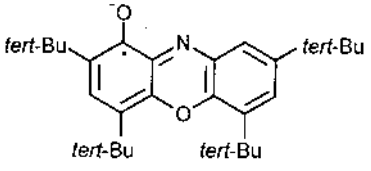
[f] Metal-based two-electron process with concomitant chloride dissociation; electrochemically reversible oxidation (metal-centered) at 0.89 V.



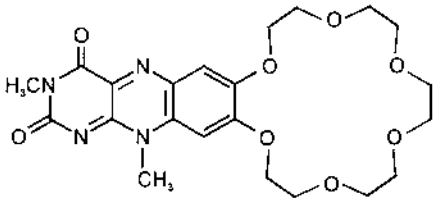
9a



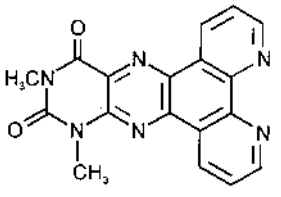
9b



9d



9c



9e

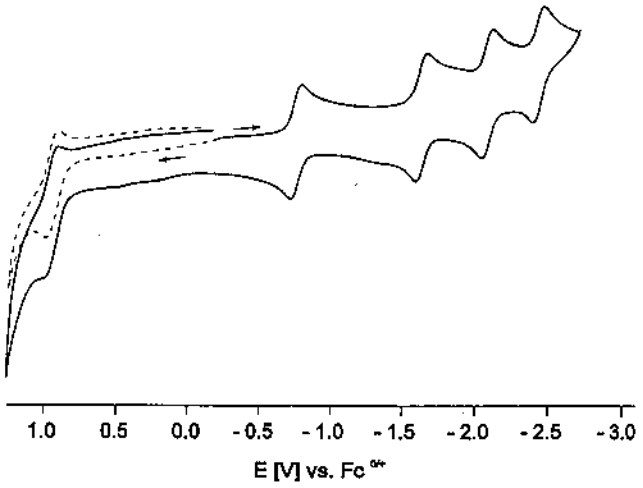


Fig. 1. Cyclic voltammogram of $[(\mathbf{4b})Ru(bpy)_2](PF_6)_2$ in THF/0.1 M Bu_4NPF_6 at 100 mV s^{-1}.

coordination mode [83]; however, the 1,10-phenanthroline/2,4-pteridinedione hybrid ligand **9e** is believed to be coordinated via the α-diimine chelating site [84].

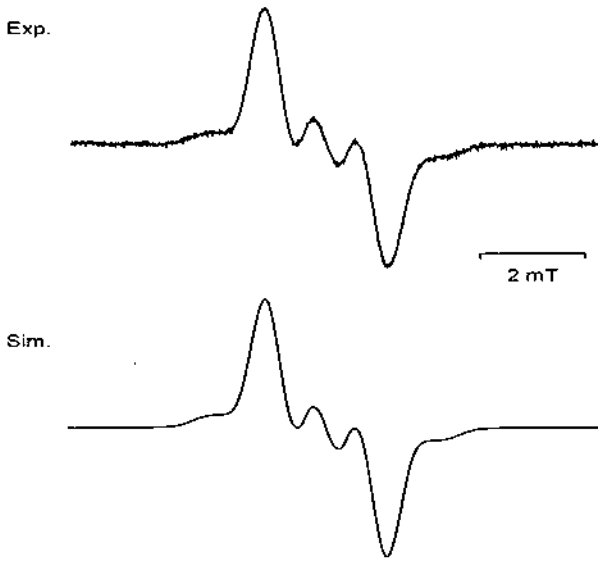
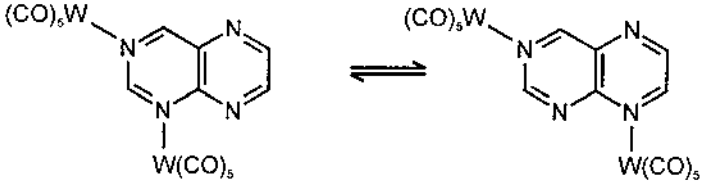


Fig. 2. (Top) EPR spectrum of $[(\mathbf{4b})Ru(bpy)_2]^{\bullet +}$ from the electrolytic reduction of the dicationic precursor in THF/0.1 M Bu_4NPF_6 at 298 K ($g = 1.9990$). (Bottom) Computer simulated spectrum with the following hyperfine coupling constants (in mT): N(5) 0.80, ^{99}Ru 0.47, ^{101}Ru 0.53; line-width 0.72 mT.

Metal coordination of flavin mononucleotide (FMN) under physiological conditions essentially involves the phosphate functions; however, a slight, indirect contribution from the heterocycle to the equilibrium constant could be established [85].

4. Complexes of pteridine ligands (pteridines, lumazines, pterins)

Metal complexes of pteridine **1** are rare. Since **1** is a highly π electron-deficient heterocyclic system it was possible to coordinate it to tungsten(0) in the complexes (**1**)$W(CO)_5$ and (μ-**1**)$[W(CO)_5]_2$ [86]. The latter compound showed NMR evidence for a fluctuating structure (Scheme 5) with the N(1) and N(8) sites competing for the binding of the second organometal fragment, basic N(3) being the primary coordination site [86].



Scheme 5.

Lumazines **3**, especially when alkyl substituted in 1,3-positions for better solubility, are fairly well-behaved ligands for coordination chemistry. Complexes with low-valent (π electron-rich) metal centers such as Re^{I}, Cu^{I} or Ru^{II} [57], with metals in more conventional oxidation states such as Cu^{II}, Zn^{II}, Cd^{II}, Hg^{II}, Ni^{II}, Co^{II}, Mn^{II}, Rh^{III} or Ir^{III} [68–72] and with metals in higher oxidation states such as W^{V}, Re^{V} and W^{VI} have been obtained with 1,3-dimethylsubstituted lumazines **3b** and **3c** [73–75]. Lumazine itself was reacted with a number of transition metal salts to yield products with either **3a** or the deprotonated form $(\mathbf{3a}\text{-}H^{+})^{-}$ as a ligand [87–89]. Corresponding crystal structures of copper(II) complexes with $(\mathbf{3a}\text{-}H^{+})^{-}$ have appeared [31,90] (Table 2).

All evidence from NMR and IR spectroscopy and from the available crystal structure analyses point to chelate coordination through N(5) and O(4). Carbonyl vibrational spectrocopy in particular has proven valuable to establish metal binding to O(4); compared to C=O(2) as a standard, the C=O(4) vibration shifts considerably and changes in intensity [57]. The binding of the d^1 fragment $W^{V}OCl_3$ to the O(4)/N(5) chelate pocket of **3b** was deduced from an analysis of paramagnetic shifts of the individual protons of coordinated **3b** [73].

The complexes of lumazines with the low-valent metal species exhibit long-wavelength absorptions in the visible due to metal-to-ligand charge transfer transitions [57]. Electrochemically, however, most of these compounds show irreversible oxida-

Table 2
Structural data[a] for the coordination site of complexes with O(4)/N(5) coordinated pterins, lumazines and flavins

Complex number	Metal fragment	Ligand(s)	M–N(5)	M–O(4)	C(4)=O(4)	O(4)–M–N(5)	Δ = [M–N(5)]–[M–O(4)]	C(4a)–N(5)	C(4)–C(4a)	Ref.
11	$[Cu^{II}(bpy)(H_2O)]^{2+}$	$(\mathbf{5d}–H^+)^{2-b}$	201.3(3)	249.9(3)	123.8(5)	73.1(1)	−48.6	n.r.	147.1(6)	[24]
12	$[Cu^{II}(bpy)]^{2+}$	$(\mathbf{3a}–H^+)^{-c}$	197.4(9)	231.6(9)	122.6(1)	78.6(4)	−34.2	135.6(2)	148.7(2)	[90]
13	Cu^+	$(\mathbf{6b})_2$	194(2)	227(2)	124(4)	79(1)	−33	132(4)	149(4)	[18]
			192(2)	221(2)	120(4)	81(1)	−29	129(4)	147(4)	
14	$[Cu^{II}(H_2O)_2]^{2+}$	$(\mathbf{3b})_2$	202.6(3)	235.3(3)	122.3(5)	77.1(1)	−32.7	133.2(4)	146.7(5)	[70]
15	Ag^{+j}	$(\mathbf{6b})_2$	230.3(6)	261.2(7)	121.0(10)	67.8(2)	−30.9	129.6(10)	149.6(11)	[14]
16	$[Cu^{II}(H_2O)_2]^{2+}$	$[(\mathbf{3a}–H^+)^-]_2$	202.2(2)	232.9(2)	n.r.	78.05(6)	−30.7	n.r.	n.r.	[31]
17	$[Mo^{IV}OL]^{-i}$	$(H^+–q^d\text{-}H_2\mathbf{5a})^+$	201.5(3)	230.2(3)	123.3(4)	72.7(1)	−28.7	134.8(4)	140.8(5)	[30]
18	$[Mo_2^{VI}O_4Cl_2]^{2+}$	$[(H_4\mathbf{5c}–H^+)^-]_2$	199.7(5)	226.9(4)	126.6(8)	74.0(2)	−27.2	137.5(9)	140.1(9)	[32]
			201.3(5)	228.7(4)	124.3(8)	–	−27.4	138.4(8)	138.9(9)	
19	$[Mo^{IV}OCl_3]^-$	$(H^+–q^d\text{-}H_2\mathbf{5a})^+$	201.3(3)	228.1(3)	126.2(5)	74.4(1)	−26.8	134.6(5)	141.7(5)	[29]
20	$[Cu^{II}(phen)]^{2+}$	$[(\mathbf{10d}–H^+)^-]_2$	201.7(4)	230.3(4)	125.0(5)	78.0(1)	−28.6	134.7(6)	144.9(7)	[26]
			206.1(3)	230.5(4)	n.r.	76.9(1)	−24.4	–	–	
21	Ag^{+k}	$(\mathbf{6b})_2$	237.3(9)	260.0(9)	124.7(19)	67.0(3)	−22.7	128.9(15)	147.4(19)	[14]
22	$[Ag^I(H_2O)]^{+l}$	**6c**	229.5(5)	252.1(5)	122.1(7)	n.r.	−22.6	130.9(7)	146.4(9)	[15]
23	$[Mo^{IV}OCl_3]^-$	$(H^+–q^d\text{-}H_2\mathbf{5e})^+$	201.7(4)	222.9(4)	127.4(7)	74.1(2)	−21.2	133.4(8)	140.1(8)	[27]
24	Ag^{+m}	$(\mathbf{6b})_2$	229.4(6)	248.8(6)	121.2(11)	n.r.	−19	128.8(10)	150.0(10)	[13]
25	$[Cu^{II}(H_2O)_2]^{2+g}$	$(\mathbf{3c})_2$	217.3(2)	235.8(2)	122.4(3)	74.4(1)	−18.5	135.0(3)	144.5(4)	[72]
26	$[Cu^{II}(H_2O)_2]^{2+h}$	$(\mathbf{3c})_2$	218.7(2)	230.3(3)	122.7(4)	75.07(9)	−11.6	134.9(4)	145.1(4)	[71]
27	$[Ru^{II}(NH_3)_4]^{2+}$	**6b**	197.9(6j	208.8(6)	126.8(10)	80.4(3)	−10.9	134.9(11)	141.6(11)	[20,21]
28	$[Cp^*Ir^{III}CI]^+$	**3b**	210.3(4)	218.6(3)	125.0(6)	76.73(14)	−8.3	135.0(6)	142.9(7)	[69]
29	$[Cp^*Rh^{III}Cl]^+$	**3b**	213.0(2)	219.2(2)	124.2(3)	77.1(1)	−6.2	134.0(4)	144.2(4)	[68]
30	$[Cp^*Ir^{III}CI]^+$	**4b**	213.8(4)	220.0(4)	124.7(6)	75.2(2)	−6.2	133.0(6)	145.0(8)	[74]
31	$[Cu^{II}(H_2O)_2]^{2+}$	$[(\mathbf{5a}–H^+)^-]_2$	197.6(2)	198.5(2)	n.r.	84.86(7)	−0.9	n.r.	n.r.	[31]
32	$[Co^{II}(H_2O)_2]^{2+}$	$[(\mathbf{10d}–H^+)^-]_2$	210.0(2)	208.6(2)	126.1(3)	80.7(1)	1.4	134.8(3)	145.7(4)	[23]
33	$[Co^{II}(H_2O)_2]^{2+g}$	$(\mathbf{3b})_2$	214.7(3)	213.2(2)	123.0(4)	78.6(1)	1.5	135.2(4)	144.4(5)	[72]
34	$[Cu^{II}(MeOH)_2]^{2+}$	$[(\mathbf{10c}–H^+)^-]_2$	200.6(5)	196.9(5)	127.8(8)	85.1(2)	3.7	134.3(8)	146.0(8)	[33]

Table 2 (*Continued*)

Complex number	Metal fragment	Ligand(s)	M–N(5)	M–O(4)	C(4)=O(4)	O(4)–M–N(5)	Δ = [M–N(5)]–[M–O(4)]	C(4a)–N(5)	C(4)–C(4a)	Ref.
35	$[Cd^{II}(NO_3)_2]^{2+}$	$(\mathbf{3c})_2$	240.6(3)	236.6(3)	122.5(5)	70.3(1)	4.0	133.7(5)	144.7(6)	[72]
36	$[Co^{II}(MeOH)_2]^{2+}$	$[(\mathbf{10c}–H^+)^-]_2$	212.6(5)	206.2(4)	128.3(7)	80.8(2)	6.4	135.1(8)	145(1)	[33]
37	$[Cu^{II}(tppb^-)]^{+e}$	$(\mathbf{5a}–H^+)^-$	203.3(3)	196.8(2)	128.2(4)	83.10(9)	6.5	134.3(4)	144.1(4)	[26]
38	$[Co^{II}(imid^f)_2]^{2+}$	$[(\mathbf{10d}–H^+)^-]_2$	217.8(2)	209.7(4)	126.2(4)	78.4(1)	8.1	133.6(7)	144.7(6)	[23]
39	$[Zn^{II}(H_2O)_2]^{2+}$	$[(\mathbf{5a}–H^+)^-]_2$	216.2(2)	205.9(2)	n.r.	80.36(8)	10.3	n.r.	n.r.	[31]
40	$[Fe^{II}(MeOH)_2]^{2+}$	$[(\mathbf{10c}–H^+)^-]_2$	218.7(3)	206.4(4)	129.1(4)	79.6(2)	12.3	134.1(s)	143.8(5)	[33]
41	$[Zn^{II}(H_2O)_2]^{2+}$	(**6d**)	221(5)	208(5)	n.r.	n.r.	13	n.r.	n.r.	[12]
42	$[W^{VI}O_2Cl_2]$	**4b**	246.2(3)	223.2(3)	124.8(4)	69.6(1)	23.0	132.3(5)	145.7(5)	[75]
43	$[Mo_2^{VI}O_5]^{2+}$	$[(\mathbf{7}–2H^+)^{2-}]_2$	232.4(6)	208.4(5)	n.r.	74.1(2)	24.0	n.r.	n.r.	[22]
			232.4(6)	208.1 (5)	n.r.	74.4(2)	24.3	n.r.	n.r.	
44	$[Cu^{II}(H_2O)_2]^{2+}$	$(\mathbf{6b})_2$	241.4(2)	204.0(2)	124.2(3)	75.86(8)	37.4	130.1(3)	147.2(4)	[16]
45	$[Cu^{II}(H_2O)_2]^{2+n}$	$(\mathbf{6c})_2$	239(2)	200(2)	128(4)	n.r.	39	131(4)	145(4)	[17]
			243(2)	200(2)	126(4)	n.r.	43	126(4)	148(4)	

[a] Bond lengths in pm (1 pm = 0.01 Å), angle O(4)–M–N(5) in degrees. Protonated or deprotonated ligands are designated as H^+–**X** or **X**–H^+, respectively.
[b] Pterin-6-carboxylate coordinates as a tridentate chelate; H_2O serves as sixth ligand.
[c] A further lumazinate anion is coordinated to $Cu^{II}(bpy)^{2+}$ via N(1).
[d] q, quinonoid.
[e] $tppb^-$, tris-(3-phenylpyrazolyl)hydroborate.
[f] imid, imidazole.
[g] Nitrate anion.
[h] Perchlorate anion.
[i] L, pyridine-2,6-bis(methanethiolato).
[j] NO_2^-/NO_3^- anions (disorder).
[k] Nitrite anion.
[l] Second silver ion coordinated to N(1), O(2) and O(2′); perchlorate anion.
[m] Nitrate anion, second silver ion coordinated to N(1) and O(2) of two ligands.
[n] Second set of numbers for species containing a second copper ion coordinated to N(1) and O(2).

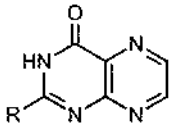
tion and reduction behavior [57,92,74]; even the metal-coordinated pterin ligands are apparently too reactive to tolerate one-electron reduction to a persistent radical intermediate. A notable exception is $[(\mathbf{3b})Ir^{III}Cl(C_5Me_5)]^{\bullet}$ [69] which—unlike the chlororhodium(III) analogue [68]—does not rapidly undergo the typical chloride-dissociative ECE reduction mechanism [91].

One- and two-electron processes can also be controlled through modifications at the heterocycles. For instance, the alkylation at N(3) was shown to effect one-electron reduction of tetraammineruthenium(II)-coordinated pterins [92].

Even non-reduced according to Scheme 2, the pterin ligands are more electron rich than the lumazines due to the replacement of one oxo function by an amino group in 2-position. Series of corresponding complexes $(N \wedge O)ML_n$ with $N \wedge O =$ lumazines, pterins and alloxazines or isoalloxazines [69,74,92] have demonstrated that the reduction potentials become less negative in that order (Table 1). Conversely, complexes of pterins are easier to oxidize than the corresponding lumazine complexes [74,92] (Table 1).

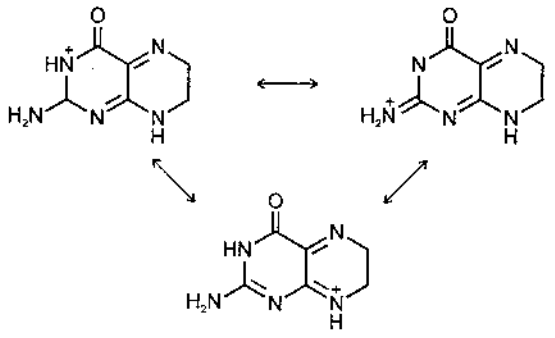
As a result, the coordination of the $[Ir^{III}Cl(C_5Me_5)]^{+}$ fragment produces reversible one-electron reduction for lumazine and alloxazine systems [69,74] but an electrochemically irreversible two-electron reduction for an N(2)-pivaloylated pterin derivative.

A major drawback in the (coordination) chemistry of pterins such as **5a** = **10a** is their notoriously poor solubility which results from multiple intermolecular hydrogen bonds. Modification of the amino function in 2-position with alkyl group containing substituents can improve this situation and compounds such as **10b**–**d** may thus be prepared for metal binding, in neutral or N(3)–H deprotonated form (Table 2) [23,26,33,34,74].

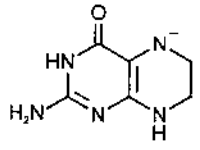


10a = 5a	R = NH_2	pterin
10b	R = NHC(O)-*tert*Bu	2-pivaloylamido-4(*3H*)pteridinone
10c	R = NMe_2	2-dimethylamino-4(*3H*)pteridinone
10d	R = SEt	2-ethylthio-4(*3H*)pteridinone

In view of the biochemical significance of the combination between partially reduced (hydrogenated) pterins and molybdenum [35] there have been a number of reports on the syntheses, reactivities and structural characterizations (Table 2) of complexes between Mo and pterins. The interpretation of the proper oxidation and protonation states has been debated; either a protonated quinonoid dihydropterin is bound to molybdenum(IV) [27,29,30] or—stoichiometrically equivalent—a deprotonated tetrahydropterin is bound to Mo^{VI} [32].



H^{-}-q-H_2**5** alternative
(Mo^{IV} binding cation)



H_4**5**-H^{+} alternative
(Mo^{VI} binding anion)

Tetrahydropterins such as H_4**5c** are indeed capable of reducing the dioxomolybdenum(VI) species $MoO_2(detc)_2$ to $Mo^{IV}O(detc)_2$ (detc = diethylthiocarbamate) [93].

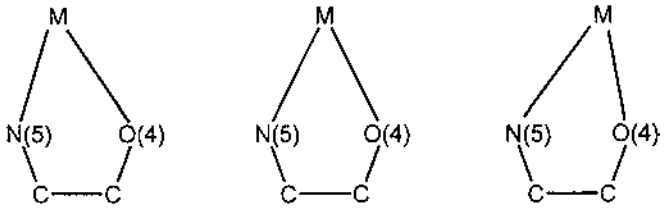
Few studies have appeared on the coordination chemistry of folic acid **5f** [64,94] or models such as **5g**. Binding of $[Ru(bpy)_2]^{2+}$ to either **5f** or to riboflavin **6c** was shown to result in labilizing of acidic protons assumed at the N(3) position [64].

5. Structural data of metal complexes

Table 2 contains a list of published structures in the field of metal coordination compounds of tricyclic (alloxazine, isoalloxazine, flavin) and bicyclic ligands (lumazines, pterins). Since almost all structures involve the O(4)–C(4)–C(4a)–N(5)–M five-membered ring chelate coordination mode, we have focused on the structural data pertaining to that chelate ring. The M–N(5), M–O(4), C(4a)–N(5), C(4)–C(4a) and C(4)=O(4) distances (1 pm = 0.01 Å) are given as is the O(4)–M–N(5) angle at the metal center. The complexes are arranged in increasing order of the difference $\Delta = d(M–N)–d(M–O)$, reflecting the changing symmetry of the chelate arrangement.

As the majority of structures contains the O(4)–C(4)–C(4a)–N(5)–M five-membered chelate ring we shall discuss the variability of this apparently simple struc-

tural motif. Although the O(4) and N(5) atoms are connected in a π-conjugated fashion (Scheme 4), the inherent asymmetry of such an α-iminoketo site is obvious. Interestingly, however, the asymmetry as quantified e.g. by the difference $\Delta = d(M–N)–d(M–O)$ can vary substantially in both directions (Scheme 6), depending on the properties of the metal and of the actual ligand with its variable electron distribution.



Scheme 6.

Steric effects can also play a decisive role as reflected by the particularly large negative deviations in Δ for complexes **11** and **12**. Compound **11** ($\Delta = -48.6$ pm) contains an effectively tridentate pterin-6-carboxylato ligand [24] and complex **12** ($\Delta = -34.2$ pm) has an additional coordination to N(1) of a neighboring lumazine ligand which creates a coordination polymer situation [89]. Considering that Jahn–Teller distorted copper(II) complexes exhibit large differences between axial and equatorial ligation it is understandable that this metal-based dichotomy can essentially determine the symmetry of the chelate arrangement (Scheme 6) which explains the occurrence of Cu^{II} complexes at both extreme ends of Table 2. Except for this special feature the general trend in Table 2 is as expected from the conventional 'hard/soft' concept: low-valent ('soft') metal centers such as Cu^{I}, Ag^{I} and Mo^{IV} bind more tightly to the nitrogen center than to O(4) ($\Delta < 0$) whereas complexes with high-valent 'hard' metal centers such as W^{VI} or Mo^{VI} exhibit shorter M–O than M–N bonds ($\Delta > 0$). The organometallic complex fragments $[M(C_5Me_5)Cl]^+$, $M = Rh^{III}$, Ir^{III} exhibit an intermediate behavior.

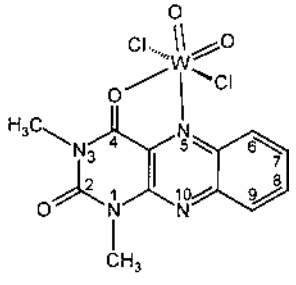


Fig. 3. Structure of [(**4b**)WO_2Cl_2] from X-ray analysis.

Absolute values vary from short M–O(4) distances of about 196 pm for $M = Cu^{II}$ (**34, 37**) to long M–O(4) bonds of more than 260 pm for $M = Ag^{I}$ (**15, 21**), and from short M–N(5) distances of about 197 pm with $M = Cu^{II}$ (**12**, **31**) and Ru^{II} (**27**) to the long M–N(5) bond of 246.2 pm for complex **42** ($M = W^{VI}$) which may be partially caused through steric interference between C(6)–H and O(=W) (Fig. 3).

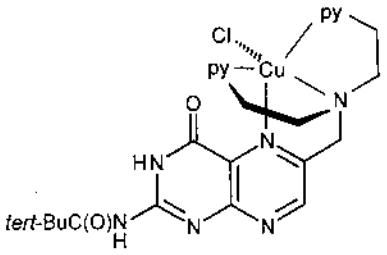
The small but noticable role of counterions on crystal and molecular structuring is evident from the series of compounds **15**, **21**, **22** and **24** or **25** and **26**. The effect of the oxidation state of the heterocyclic ligand can be studied by examining the compounds **17**–**19** and **23**, all of which contain reduced pterin ligands. In those cases the N(5) center becomes more basic which explains the shortness of corresponding M–N(5) bonds.

The bite angles O(4)–M–N(5) depend mainly on the size of the metal center, small values down to 67° were found for Ag^{I} complexes and large angles up to 85° for compounds with tightly bound Cu^{II}. Bond lengths within the π centers of the chelate ring show deviations if the ligand is partially reduced. Compounds **17-19** and **23** thus exhibit shortened C(4)–C(4a) but lengthened C(4)–O(4) and C(4a)–N(5) bonds—a familiar pattern in this kind of chelate redox chemistry [59].

The molybdopterin (tungstopterin) coenzymes **8** [35] and a few model complexes [13,15,17,19,24,34,96] do not show (exclusively) the O(4)–N(5) chelate structure. As was long anticipated [1,35], the former contain Mo or W bound by a dithiolene side function of the actual pterin system (**8**) which conveys an oxidation state ambiguity [1,60] and, most probably [1,35], a special electron transfer function to this active entity of the O-transferring enzymes. Model structures involving dicyclopentadienylmolybdenum bound to quinoxaline-connected ene-dithiolate and -trithiolate entities have been reported [95].

Other exceptions from the O(4)–N(5) coordination pattern merit mentioning: With soft, heavy lead(II) the 10-methylisoalloxazine ring system **6b** binds mainly through the O(2) (246(2) and 263(2) pm) and albeit very weakly through the N(1) donor atoms (299(2) pm) in a structurally complicated manner, involving counterions and additional water molecules [19]. This N(1)/O(2) 'secondary metal binding site' of the flavin system is also used by Ag^{+} in complexes **22** and **24** and by Cu^{2+} in **45**.

In an effort to utilize the amino function in the pterin side chain of folic acid models Karlin and coworkers have managed to characterize structurally species **46** and **47** in which the O(4) donor center is not involved in chelate coordination [34,96]. A related approach to model more closely the folic acid situation (**5f**) has resulted in the synthesis of 6-[*N*-(*p*-tolyl)-aminomethyl]-2-pivaloylpterin (**5g** [74]) the coordination chemistry if which is being explored.



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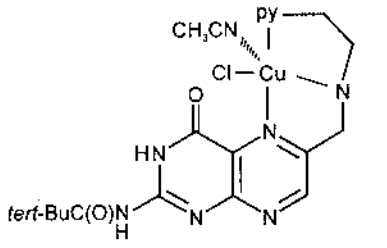

47 (py = 2-pyridyl)

6. Outlook

In spite of the available chemical and spectroscopic information and the impressive list of structures there are a number of uncharted areas remaining in the metal coordination chemistry of heterocyclic coenzymes. These include a better documentation of metal binding by various reduced species such as flavosemiquinones, flavohydroquinones, tetrahydropterins or pterin radical intermediates. Furthermore, the exploration of the coordination chemistry of (tetrahydro)folate and reduced molybdopterin (pyranopterin [35,97]) has only just begun. In the biochemical context, the requirements, mechanisms and significance of the interactions between metal centers and the coenzymatic components remain very sketchy, despite the recent progress in protein crystallography [35,51–53]. This unsatisfactory state clearly poses a challenge for theory and for better, more ingenious modelling with elaborate organic ligands and their metal compounds.

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