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Preparations and Properties of Transition-Metal Pterin Complexes. Models for the Metal Site in Phenylalanine Hydroxylase

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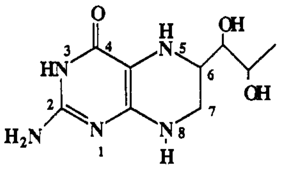
Syntheses and physical properties of pterin and pteridine complexes of first-row transition metals are described. Characterization used single-crystal x-ray diffraction, spectroscopic, and microanalytical methods. These data all indicate that pterin and pteridine ligands chelate via oxygen and nitrogen atoms. Three copper complexes have been structurally determined. Cu(tppb)(pterin) (**1**) [tppb$^-$ = tris(3-phenylpyrazolyl)hydroborate] crystallizes in the triclinic space group $P\bar{1}$ with cell dimensions a = 11.835 (2) Å, b = 12.062 (2) Å, c = 12.831 (2) Å, α = 66.91 (1)°, β = 83.68 (1)°, and γ = 77.10 (1)° defining a volume of 1641.9 Å^3 for Z = 2. The five-coordinate cupric ion has a square-pyramidal geometry, and the pterin ligand occupies two equatorial positions. Pterin coordination in **1** significantly differs from the only extant report of a cupric pterin complex both in orientation and in Cu–O bond strength. Cu(ethp)$_2$(phen) (**4**) [ethp = 2-(ethylthio)-4-oxopteridine; phen = 1,10-phenanthroline] also crystallizes in the triclinic space group $P\bar{1}$. Unit cell parameters a = 12.414 (2) Å, b = 12.882 (2) Å, c = 11.371 (2) Å, α = 112.55 (2)°, β = 92.58 (1)°, and γ = 83.96 (1)° define a volume of 1670.1 Å^3 for Z = 2. The copper coordination sphere has an elongated octahedral geometry defined by four equatorial nitrogen atoms (two from the pteridines and two from phenanthroline) with axial positions filled by oxygen atoms of the pteridine chelates. The third structure reported is for the compound [Cu(phen)$_2$(acetate)][acetate-H-ethp] (**5**). In this structure, the pteridine does not chelate copper but is incorporated into the anionic counterion. The compound crystallizes in the monoclinic cell $P2_1/c$ with parameters a = 11.755 (2) Å, b = 19.079 (2) Å, c = 16.329 (2) Å, and β = 110.36 (1)°, resulting in a cell volume of 3343.6 Å^3 for Z = 4. The copper atom is coordinated in a distorted square-pyramidal geometry composed of two phenanthroline chelates and one monodentate acetate ligand. The anion can be formulated as an acetate hydrogen-bonded to the hydroxyl group of the pteridine enol tautomer. A comparison of EPR parameters for the copper complexes reported in this manuscript with previous data for copper pterin complexes reveals that only the value of $A_{\|}$ is sensitive to variation in copper environments. Spectroscopic and structural data point to a stronger metal–pterin interaction for equatorially bound pterinate ligands. Preliminary results of copper(II) reduction by tetrahydropterin are also presented.

Introduction

The identification of pterin cofactors in several metalloenzymes has renewed interest in pteridine coordination to transition metals. These metalloenzymes can be separated into two classes according to their pterin cofactors. The first class uses the tetrahydropterin cofactor, biopterin, and ferrous or cuprous ions to catalyze the hydroxylation of the aromatic amino acids phenylalanine, tyrosine, and tryptophan.[1]



tetrahydrobiopterin

The second class consists of the oxo–molybdenum enzymes for which the pterin cofactor is not yet unambiguously identified.[2] We have been studying reactions between transition metals and pterins to mimic both the metal environment and reactivity of the metal site in these enzymes.[3] In this paper, we report our progress in modeling the metal site in bacterial phenylalanine hydroxylase [PAH].

Spectroscopic studies on the copper site in PAH identify it as a type 2 cupric ion in a tetragonal coordination environment of several nitrogen donors.[4] Evidence from ESR experiments suggests an interaction between the pterin cofactor and the cupric ion through coordination by the nitrogen in position 5.[5] Because tetrahydropterins are known to reduce cupric to cuprous ions,[6,22] the pterin coordinating Cu^{2+} in this experiment is likely to be at the semireduced state.

Yamauchi et al. have recently reported the first structure of a cupric pterin complex obtained from reactions in aqueous media.[7] Our concurrent investigations of metal pterin chemistry in nonaqueous solution show different behavior. Below we describe the syntheses and structures of three cupric pteridine compounds, their spectroscopic characterization by infrared, visible, and EPR methods, and preliminary results of tetrahydropterin reductions of cupric complexes.

Experimental Section

All reagents used in this work were purchased from Aldrich Chemical Co. except as noted below. Solvents purchased from Aldrich Chemical were HPLC grade and not purified before use. Potassium tris(3-phenylpyrazolyl)hydroborate [K$^+$tppb$^-$] was prepared according to the procedures reported by Trofimenko et al.[8] Tetraethylammonium pterinates were prepared as previously described.[9] Infrared spectra of samples as KBr disks were recorded on a Perkin-Elmer Model 683 instrument and are referenced to the 1601.2-cm^{-1} absorption of polystyrene. Microanalyses were performed by M-H-W Labs, Phoenix, AZ. X-ray diffraction data was collected on an Enraf-Nonius CAD4 diffractometer at the University of Pennsylvania. The full structural analysis of Cu-

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(9) Tetraethylammonium pterinate salts were made by addition of 1 equiv of tetraethylammonium hydroxide to a slurry of the pterin in methanol. The pterin dissolves as the deprotonation proceeds to give a bright yellow solution. Transferring the reaction solution to diethyl ether precipitates the [TEA][pterinate] salt.

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(tppb)(pterin) (**1**) was determined at Bryn Mawr College, and analyses of complexes Cu(ethp)$_2$(phen) (**4**) and [Cu(phen)$_2$(acetate)][acetate-H-ethp] (**5**) were completed at the University of Pennsylvania. Electronic spectra were recorded on a Perkin Elmer Hitachi 200 or a Hewlett-Packard 8452 spectrophotometer. Solution conductivities were measured by using a Barnstead PM-70CB conductivity bridge equipped with a Yellow Springs Instruments 3403 dip cell. Magnetic susceptibilities were obtained by the Gouy method using HgCo(SCN)$_4$ as a calibrant or by the Evans method. Corrections for the diamagnetic contributions from the ligands were calculated by using Pascal's constants.[10]

Syntheses. Cu(tppb)(pterin) (1). Cu(acetate)$_2$·2H$_2$O (1.00 mmol, 0.200 g) and K[tppb] (1.00 mmol, 0.480 g) were dissolved separately in a minimum amount of methanol and combined. To this solution was slowly added [TEA][pterinate] (1.00 mmol, 0.200 g) also dissolved in a minimum volume of warm methanol. The solution was stirred for several minutes. Any brown precipitate formed at this stage was removed by filtration through a glass frit. Green crystals formed from the methanolic solution after several days and were recrystallized from chloroform and ethyl ether. Yield: 0.28 g (38%). Anal. Calcd for Cu(tppb)(pterin)·CHCl$_3$·CH$_3$OH, $C_{35}H_{31}CuCl_3O_2N_{11}B$: C, 51.37; H, 3.82; N, 18.83. Found: C, 51.09; H, 3.63; N, 18.97.

Cu(tppb)(ethp) (2). This compound was made by following the procedure for **1** except that ethp was dissolved in warm DMF. Green needle-shaped crystals obtained from the reaction solution were recrystallized from chloroform and methanol. Yield: 70%. Anal. Calcd for $C_{35}H_{29}CuSON_{10}B$: C, 59.03; H, 4.11; N, 19.67; S, 4.50. Found: C, 58.75; H, 4.56; N, 19.02; S, 4.48.

Cu(ethp)$_2$(H$_2$O)$_2$ (3). Cu(acetate)$_2$·2H$_2$O (0.500 mmol, 0.100 g) and ethp (1.000 mmol, 0.208 g) were dissolved separately in a minimum amount of warm DMF. The solutions were cooled, and then the copper solution was added slowly to the ligand solution to produce a yellow-brown color. A fine brown precipitate was removed by filtration. The lime-green filtrate yielded lime green plate crystals after several days. The product was recrystallized from DMF and ether. Yield: 0.15 g (58%). Anal. Calcd for $C_{16}H_{18}CuS_2O_4N_8$: C, 37.39; H, 3.53; N, 21.80; S, 12.48. Found: C, 38.05; H, 3.49; N, 21.69; S, 12.30.

Cu(ethp)$_2$(phen) (4). This compound was obtained in 40% yield by following the procedure for **3** with addition of 1 equiv of phenanthroline. **4** can also be formed in 76% yield by adding 1 equiv of phenanthroline to Cu(ethp)$_2$(H$_2$O)$_2$ in dmf. **4** is isolated as emerald green needle crystals. Anal. Calcd for $C_{28}H_{22}CuS_2O_2N_{10}$: C, 51.09; H, 3.37; N, 21.28; S, 9.74; Cu, 9.65. Found: C, 50.68; H, 3.81; N, 21.56; S, 10.04; Cu, 9.96.

[Cu(phen)$_2$(acetate)][acetate-H-ethp] (5). Cu(acetate)$_2$·2H$_2$O (1.500 mmol, 0.298 g), 1,10-phenanthroline (3.000 mmol, 0.540 g), and ethp (1.500 mmol, 0.312 g) were dissolved separately in minimum volumes of warm DMF. The phenanthroline solution was added to the copper acetate, and then the ethp ligand was added dropwise. The final solution color is green. Turquoise prismatic crystals of **5** formed after several days. Yield: 0.62 g (78%).

M(ethp)$_2$(H$_2$O)$_2$, M(tppb)(Me$_2$pterin), and M(tppb)(ethp) (M = Mn^{II}, Co^{II}, Ni^{II}, Zn^{II}). These complexes were obtained by the above procedures developed for Cu^{II} where M^{II}(acetate)$_2$ reagents were substituted for cupric acetate.

Fe(ethp)$_2$(MeOH)$_2$·MeOH. In an inert-atmosphere box, ethp (0.832 g, 4 mmol), was dissolved in 2 mL of dmso and 10 mL of methanol. Four equivalents of NaH were added to deprotonate the ligand, yielding a yellow solution. The ethp solution was added to a solution of anhydrous ferrous chloride (0.252 g, 2 mmol) dissolved in 5 mL of methanol, producing an immediate color change to deep purple. A 0.880-g (83%) yield of solid precipitated on standing. Anal. Calcd for Fe(ethp)$_2$(MeOH)$_2$·MeOH, $C_{19}H_{26}FeS_2O_5N_8$: C, 40.29; H, 4.63; N, 19.78; S, 11.32. Found: C, 39.10; H, 4.74; N, 19.64; S, 10.91.

Fe(dmp)$_2$(H$_2$O)$_2$·$^1/_2$dmso and Fe(hp)$_2$(H$_2$O)$_2$ can be prepared by the method described for Fe(ethp)$_2$(MeOH)$_2$·MeOH. Fe(dmp)$_2$(H$_2$O)$_2$·$^1/_2$dmso and Fe(hp)$_2$(H$_2$O) are isolated as a red-purple and blue powders, respectively. Anal. Calcd for Fe(dmp)$_2$(H$_2$O)$_2$·$^1/_2$dmso, $C_{15}H_{27}FeS_{0.5}O_{4.5}N_{10}$: C, 39.93; H, 4.53; N, 27.39; S, 3.14. Found: C, 36.71; H, 4.68; N, 25.3; S, 2.80.

Crystal Structures of Cu(tppb)(pterin) (1), Cu(ethp)$_2$(phen) (4), and [Cu(phen)$_2$(acetate)][acetate-H-ethp] (5). Collection and Reduction of X-ray Data. Crystals suitable for x-ray diffraction were obtained for each compound as follows. **1** crystallized as lime green prisms from a chloroform solution of the copper complex layered with diethyl ether. **4** crystallized as emerald green needles from evaporation of a dimethylformamide solution. Diffraction quality crystals of **5** were obtained from the dimethylformamide reaction solution as large turqoise prisms. Since coating these copper complexes with epoxy resin caused crystal degradation, all three crystals were mounted in capillary tubes sealed with epoxy. The crystal of **1** was sealed with a drop of the mother liquor in the capillary to prevent solvent loss from the crystal. Diffraction data were côllected at room temperature on an Enraf-Nonius CAD4 diffractometer using molybdenum radiation and a graphite monochromator. Crystallographic data for the three compounds are listed in Table IV. Unit cell parameters were determined by using machine-centered reflections in the region 20° ≤ 2θ ≤ 25°. The data were processed with programs from the 1985 version of the Structure Determination Package (SDP) on a VAX 1170 computer at the University of Pennsylvania and on the VAX 8200 at Bryn Mawr College.[11]

Structure Solution and Refinement. The positions of the copper atoms were located by Patterson methods. Subsequent cycles of least-squares refinement and difference Fourier calculation were used to locate the remaining non-hydrogen atoms. In the final stages of refinement hydrogen atom positions were calculated assigning C–H or N–H distances of 0.95 Å. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were assigned thermal parameters of 1.3 × those of adjacent carbon or nitrogen atoms. During the refinement of **1** positions of significant electron density located from a difference Fourier calculation were identified at nonbonding distances from the copper complex. These were therefore assigned as solvent atoms present in nonstoichiometric amounts. The refinement was the same (as judged by values of R and R_w and a difference Fourier map) whether these two atoms were assigned as chlorine atoms at 0.500 occupancy or oxygen atoms at full occupancy. The structure was completed by using the first assignment. Compound **4** crystallized with one dimethylformamide (DMF) molecule in the lattice and atomic positions of this molecule were satisfactorily located and refined.

EPR Spectroscopy. EPR spectra were obtained at the University of Georgia Center for Metalloenzyme Studies. A Bruker ER200D spectrometer equipped with an Oxford Instruments ESR9 helium cryostat and a Bruker ER1600 computer. All EPR samples were prepared in DMF and frozen in liquid nitrogen. Samples were run under nonsaturating conditions at 20 K at microwave power 2 mW and 1 G modulation amplitude.

Results

Syntheses. Synthesis of first-row transition-metal pteridine and pterin complexes occurs readily and our procedures utilize two methods. The first method is illustrated in preparations of complexes M(ethp)$_2$(L)$_2$ and M(tppb)(ethp).[12] Addition of a DMF solution of ethp to a metal acetate salt in the presence of other ligands such as phen or tppb causes pteridine deprotonation and coordination forming a neutral complex. These reactions are unsuccessful if metal chloride rather than acetate reagents are used, demonstrating the role of the acetate ion as base. If amines are added to reactions of metal chlorides with pteridines, some of the expected product forms, but the isolated material is considerably less pure, probably due to competing amine coordination. Metal acetates provide optimal conditions in these syntheses as a result of the weaker coordinating ability of acetate. The counteranion (acetate-H-ethp) in **5** that was identified from the structural determination provides evidence for acetate serving as a base in these reactions. A second method has been developed

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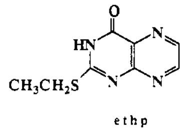
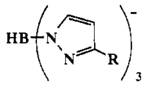
(10) Drago, R. S. *Physical Methods in Chemistry*; Saunders: Philadelphia, PA, 1977; p 426.

(11) Scattering factors are taken from: Cromer, D. T.; Waber, J. T. In *International Tables for X-ray Crystallography*; Ibers, J. A., Hamilton, W., Eds.; Kynoch Press: Birmingham, England, 1974; Vol. IV. $I = S(C + RB)$ and $\sigma^2(I) = (C + R^2B)$, where I = intensity, C = total integrated peak count, R = ratio of scan count time to background count time, and B = total background count time. The weighting scheme used in the least-squares minimization of the function was $\sum w(|F_o| - |F_c|)^2$ where $w = 1/\sigma(F_o)^2$ and $\sigma(F_o) = [\sigma^2(F_o) + \rho^2 F_o{}^2]^{1/2}$ with ρ assigned a value of 0.01. Expressions for the residuals are $R = \sum||F_o| - |F_c||/\sum|F_o|$ and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w(F_o)^2]^{1/2}$. The "goodness of fit" equation is GOF = $\{\sum w(|F_o| - |F_c|)^2/(\mathrm{NO} - \mathrm{NV})\}^{1/2}$, where NO is the number of observations and NV is the number of variables. The anisotropic thermal parameter is of the following form: $\exp[-0.25(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$.

(12) Structures and abbreviations used for ligands in this manuscript are



ethp



tppb: R= Ph
tbbp: R= tert-butyl

Table I. Infrared Data for Metal Pteridinate Complexes

complex	ν_{B-H}, cm^{-1}	$\nu_{C=O,C=N}$, cm^{-1}
Cu(tppb)(pterin) (**1**)	2478 w	1620 m, 1595 vs, 1535 s, 1513 s, 1490 s, 1455 s, 1358 s
Cu(ethp)$_2$(phen) (**4**)		1673,^{a} 1587 vs, 1508 sh, 1490 s, 1424 sh, 1414 s
[Cu(phen)$_2$(acetate)]$^+$[acetate-H-ethp]$^-$ (**5**)		1710,^{b} 1610 s, 1590 s, 1518 s, 1485 vs, 1432 s, 1401 s, 1330 s
Co(tppb)(Me$_2$pterin)	2455	1620 m, 1589 s, 1519 vs, 1490 vs, 1460 vs, 1437 s
Ni(tppb)(Me$_2$pterin)	2490	1616 m, 1585 vs, 1525 sh, 1490 s, 1465 s, 1450 s, 1420 s
Cu(tppb)(Me$_2$pterin)	2495 w	1615 sh, 1587 vs, 1536 s, 1492 s, 1468 s, 1450, 1423, 1363 s, 1333 s
Zn(tppb)(Me$_2$pterin)	2490	1620 sh, 1585 vs, 1525 sh, 1492 s, 1467 s, 1450 s, 1426 s
Co(tppb)(ethp)	2492	1578 s, 1510 sh, 1490 vs, 1465 s, 1410 s, 1360 s, 1340 s
Ni(tppb)(ethp)	2495	1585 s, 1515 s, 1492 vs, 1466 s, 1412 s, 1362 s, 1340 s
Cu(tppb)(ethp) (**2**)	2495	1586 s, 1519 vs, 1501 vs, 1468 m, 1415 m, 1363 m
Zn(tppb)(ethp)	2495	1578 s, 1490 vs, 1466 s, 1411 s, 1362 s, 1340 s
Mn(ethp)$_2$(H$_2$O)$_2$		1580 s, 1499 vs, 1408 s, 1334 s
Fe(ethp)$_2$(H$_2$O)$_2$		1580 s, 1515 sh, 1495 s, 1411 s
Ni(ethp)$_2$(H$_2$O)$_2$		1588 s, 1500 vs, 1410 s, 1344 s
Cu(ethp)$_2$(H$_2$O)$_2$ (**3**)		1586 s, 1508 s, 1490 s, 1411 s, 1348 s
Fe(hp)$_2$(H$_2$O)$_2$		1586 s, 1530 br, 1415 s, 1334 s
Ni(hp)$_2$(H$_2$O)$_2$		1595 s, 1532 s, 1510 sh, 1420 s, 1333 s
Fe(Me$_2$pterin)$_2$(H$_2$O)$_2$		1612 sh, 1585 s, 1521 vs, 1492 s, 1460 m, 1434 s, 1392 m, 1343 m

^{a} $\nu_{C=O}$ of DMF solvent. ^{b} $\nu_{C=O}$ of uncoordinated C=O of ethp.

for preparing metal–pterin complexes using pterins having low solubility in DMF. These pterins can be solubilized in methanol by deprotonation with tetraethylammonium hydroxide or sodium hydride. [TEA$^+$][pterinate$^-$] salts can be isolated as crystalline solids. Combination of these [TEA][pterinate] salts in methanol with metal reagents (chloride, nitrate, or perchlorate salts) yields the desired product.

Phenanthroline was incorporated into the above synthetic procedures to better approximate the coordination environment of copper in PAH since previous experiments indicate the presence of two nitrogen atoms in addition to that from pterin.[4] The choice of phenanthroline was anticipated to limit the number of pterins bonding copper and to allow formation of a ternary complex [Cu^{II}(phen)$_{1\text{ or }2}$(pterinate)]$^+$. All attempts to obtain ternary complexes by variation of the solution composition failed. In every case the products isolated contained either two pteridine chelates (cf. complex **4**) or two phenanthroline chelates but no coordinated pteridine (cf. complex **5**). It is evident that solubility determines which product is obtained from a dynamic equilibrium among several species since we find recrystallization of [Cu(phen)$_2$(acetate)][acetate-H-ethp] yields a mixture of [Cu(phen)$_2$(acetate)][acetate-H-ethp], Cu(ethp)$_2$(phen), and Cu(ethp)$_2$(H$_2$O)$_2$.

The prevalent formation of neutral species from our reaction mixtures and the inability of phenanthroline to limit pteridine coordination led us to attempt reactions employing the tridentate, anionic N-donor ligand, tris(pyrazolyl)hydroborate, HB(pyz)$_3^-$. We selected the recently reported[8] 3-phenyl derivative to avoid formation of stable bis complexes M^{II}(HB(pyz)$_3$)$_2$. We refer to this ligand using the abbreviation "tppb". Complexes of the desired stoichiometry M(tppb)(pterin) (M = Co^{II}, Ni^{II}, Cu^{II}, Zn^{II}) were easily made and characterized. The phenyl substituents and the neutral overall charge on the complexes led to improved solubility properties so that spectral analyses and recrystallizations could be performed in less polar solvents (CHCl$_3$, CH$_2$Cl$_2$, acetone, acetonitrile) than have previously been employed with pteridine and flavin complexes. The analogous ferrous complex could not be obtained due to formation of the bis complex, Fe(tppb)$_2$.[13] Attempts using the bulkier tris(*tert*-butylpyrazolyl)hydroborate ligand[8] with Fe(II) in reactions with pterins were also unsuccessful. Here the steric requirements of the pyrazolylborate ligand appear to prevent pterin coordination.

Physical data on these new metal pterinate complexes are listed in Tables I–IV. Solution conductivities measured in acetone or acetonitrile have values well below the range normally found for 1:1 salts[14] and indicate little dissociation occurs in these solvents. Infrared data are nearly identical within any one homologous set of complexes, (cf., M(tppb)(ethp), M = Co, Ni, Cu, Zn) and are consistent with similar anionic pteridinate binding in each case. Complexes containing the tridentate tppb ligand show a weak absorption near 2490 cm^{-1} due to ν_{B-H}. Magnetic susceptibility measurements on the ferrous, cobaltous, and nickel pterin complexes indicate that the electronic state of these metal ions is high spin.[15]

Electronic spectral absorptions and molar absorptivity constants are consistent with the molecular formulations. Spectra for tppb complexes were obtained from chloroform solutions; all other complexes were studied as dimethylformamide solutions. Absorptions in the region 400–800 nm have weak absorptivities (ϵ < 150 M^{-1} cm^{-1}) characteristic of d–d transitions, with the striking exception of the ferrous complexes. Pteridinate complexes of Fe^{II} have intense absorptions between 500 and 600 nm, and the magnitude of the molar absorptivities suggests these absorptions originate from a charge-transfer process, probably of the metal-to-ligand type. Absorption energies and molar absorptivities for other metal complexes provide clues about the likely solution structure in each case. On the basis of comparisons with the large body of data available for Cu^{II} complexes,[16] solution spectra of Cu(tppb)(pterin) and Cu(ethp)$_2$(phen) indicate that the structures observed in the crystalline solid are retained in solution. Since the spectrum of Cu(tppb)(ethp) is very similar to that of Cu(tppb)(pterin), the likely geometry of Cu(tppb)(ethp) is also square pyramidal. The similar spectra observed for Cu(ethp)$_2$(phen) and Cu(ethp)$_2$(H$_2$O)$_2$ likewise predict an elogated tetragonally distorted octahedral geometry for Cu(ethp)$_2$(H$_2$O)$_2$. Spectral data for the Co(tppb) complexes resemble those reported for five-coordinate Co^{II} compounds.[17] All complexes have absorptions in the ultraviolet spectral region due to transitions involving the pterinate ligand and reproduce results reported by one of us in previous studies on cobaltous bis(pterinate) complexes.[3] We note that the transitions due to the ethp anion in the low-energy UV region observed for the five-coordinate tppb complexes, M(tppb)(ethp) (M = Co, Ni, Cu), are slightly shifted to longer wavelengths as compared to those for the (ethp) complexes of the same metals (cf., λ_{max} = 385 nm in Cu(tppb)(ethp) and 355 nm in Cu(ethp)$_2$(phen); for $\Delta\lambda_{max}$ = 30 nm).

EPR parameters for new copper complexes reported in this paper are given in Table III. Spectra obtained from frozen solutions of the copper complexes have the well-documented fea-

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(13) Fe(tppb)$_2$ can be prepared by addition of 2 equiv of K(tppb) to ferrous chloride or acetate in methanol under an inert atmosphere. Fe(tppb)$_2$ immediately precipitates as a white, crystalline solid. Anal. Calcd for Fe(tppb)$_2$, C$_{54}$H$_{44}$FeN$_{12}$B$_2$: C, 69.10; H, 4.72; N, 17.91. Found: C, 69.14; H, 4.80; N, 17.92.

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Table II. Physical Data on Metal Pteridinate Complexes

complex	$\lambda_{\max}$ (ϵ), nm (M^{-1} cm^{-1})	color	μ_{eff}, μ_B	conductivity (solvent), Ω^{-1} mol^{-1} cm^2
Cu(tppb)(pterin) (**1**)	688 (37) 387 (5260) 312	green		13.4 (acetone)
Co(tppb)(Me$_2$pterin)	695 (18) 560 (32) 535 (31) 380 (2400) 307 (1450)	burgundy red		
Ni(tppb)(Me$_2$pterin)	655 (14) 375 (2200) 310 (1400)	green		
Co(tppb)(ethp)	685 (75) 565 (36) 540 (34) 395 (6500) 320 (8000)	burgundy red	5.0	1.6 (acetone)
Ni(tppb)(ethp)	627 (17) 380 (7290) 338 (8330)	green	4.2	1.3 (acetone)
Cu(tppb)(ethp) (**2**)	695 (35) 385 (5100) 343	green		10.4 (acetone) 3.6 (acetonitrile)
Zn(tppb)(ethp)	367 (7500)	yellow		2.9 (acetone)
Cu(ethp)$_2$(phen) (**4**)	705 (163) 355 273	emerald green		
Mn(ethp)$_2$(H$_2$O)$_2$	360 270	pink	5.6	
Fe(ethp)$_2$(MeOH)$_2$	586 (6200) 356 (19000) 270 (50000)	indigo blue	3.6	
Fe(Me$_2$pterin)$_2$(H$_2$O)$_2$	560 (2300) 370 (4700) 270 (8900)	dark rose		
Ni(ethp)$_2$(H$_2$O)$_2$	365 (16000)	yellow	3.1	
Cu(ethp)$_2$(H$_2$O)$_2$ (**3**)	702 (60) 360 264	lime green		

Table III. EPR Parameters for Copper Pteridinate Complexes

	$g_\perp$	$g_\parallel$	$A_\parallel$, G	A_N, G[a]
Cu(ethp)$_2$(H$_2$O)$_2$	2.06	2.28	164.5	11
Cu(ethp)$_2$(phen)	2.07	2.28	171.5	14
Cu(tppb)(pterin)	2.06	2.28	158	
Cu(tppb)(ethp)	2.06	2.28	162	11
Cu(II) in PAH[b] + H$_4$pterin	2.06	2.27	166	13
Cu(bipy)(PC)(H$_2$O)[c]	2.06	2.27	169	
Cu(bipy)(PC)(imid)[c]	2.05	2.25	181	

[a] In $g_\perp$ region. [b] Reference 5. [c] Reference 20.

tures[16] of axial symmetry where $g_\parallel > g_\perp$, indicating the copper is in a $x^2 - y^2$ ground state. While the values of $g_\parallel$ and $g_\perp$ are essentially identical for all four copper complexes **1–4**, the copper hyperfine tensor observed in the $g_\parallel$ region shows significant variation, adopting values from 158 to 171 G. Nitrogen hyperfine splitting is apparent in the $g_\perp$ region for the complexes Cu(tppb)(ethp) (**2**) and Cu(ethp)$_2$(phen) (**4**). Complex **2** has a seven-line pattern from nitrogen hyperfine coupling corresponding to the three nitrogen atoms in the equatorial plane. Nine lines are observed for **4** as expected for four N-donor atoms located in the equatorial plane.

Crystal Structures of Cu(tppb)(pterin), Cu(ethp)$_2$(phen), and [Cu(phen)$_2$(acetate)][acetate-H-ethp]. The structure of Cu(tppb)(pterin) (**1**) is illustrated in Figure 1 and shows the distorted square-pyramidal coordination geometry around copper. The donor atoms in the basal plane consist of the oxygen (O4) and a nitrogen (N5) from the pterin and two nitrogen atoms of tppb. The axial site is occupied by a nitrogen of the third pyrazolyl ring.

The degree of distortion from ideal square-pyramidal geometry in **1** can be estimated by inspection of bond angles and distances in Table VIII. The O–Cu–N and N–Cu–N angles range from 83 to 103°, and those angles having the largest deviation from 90° involve atom O4. The small bite of the pterin ligand (83°) and the skewed dihedral angle of the pterin ligand to the idealized equatorial plane are responsible for the nonideal geometry. The pterin plane makes a 14° dihedral angle to the plane formed by atoms N5, N9, N11, and Cu, placing atom O4 0.38 Å below the equatorial plane. This skewed relationship of the pterin ligand to the equatorial plane may be due to a stacking interaction between one phenyl ring on tppb (composed of atoms C18, C19, C20, C21, and C22) and the pterin. The dihedral angle associated with this interaction is 10°. A second distortion caused by the stacking interaction is the nonorthogonal dihedral angle (73°) between the "axial" pyrazolyl ligand (atoms N13, N14, C15, C16, and C17) to the equatorial plane (atoms Cu, N5, N9, and N11).

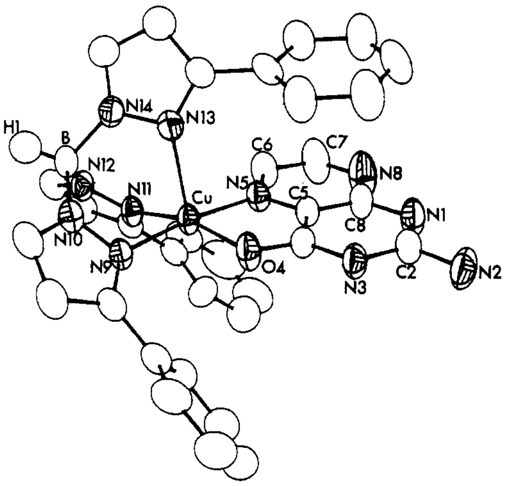

Figure 1. Ortep drawing of Cu(tppb)(pterin) (**1**).

Table IV. Crystallographic Parameters for Data Collection and Structure Refinement

	Cu(tppb)(pterin) (**1**)	Cu(ethp)$_2$(phen) (**4**)	[Cu(phen)$_2$(acetate)][(acetate-H-ethp)] (**5**)
formula	$CuClO_1N_{11}C_{33}BH_{26}$[a]	$CuS_2O_3N_{11}C_{31}H_{29}$[a]	$CuSO_5N_8C_{36}H_{30}$
fw	702.45	731.32	750.30
space group	triclinic $P\bar{1}$ (No. 2)	triclinic $P\bar{1}$ (No. 2)	monoclinic $P2_1/c$ (No. 14)
a, Å	11.835 (2)	12.414 (2)	11.755 (2)
b, Å	12.062 (2)	12.882 (2)	19.079 (2)
c, Å	12.831 (2)	11.371 (2)	16.329 (2)
α, deg	66.91 (1)	112.55 (2)	
β, deg	83.68 (1)	92.58 (1)	110.36 (1)
γ, deg	77.10 (1)	83.96 (1)	
vol, Å^3	1641.9	1670.1	3343.6
Z	2	2	4
d(calc), g/cm^3	1.421	1.454	1.451
μ, cm^{-1}	7.916	8.23	7.48
radiation	Mo Kα, 0.71073 Å		
scan range, deg	$4.0 < 2\theta < 50$	$4.0 < 2\theta < 50$	$4.0 < 2\theta < 50$
octants collcd	$+h,\pm k,\pm l$	$+h,\pm k,\pm l$	$+h,+k,\pm l$
scan width, deg	1.30	1.30	1.30
bkgd	25% of full peak width on each side		
no. of unique data	5768	7999	6024
no. of data with $I > 3\sigma(I)$	4626	3839	2598
no. of variables	432	433	460
R	0.043	0.053	0.049
R_w	0.059	0.060	0.052
goodness of fit	1.891	1.376	1.226

[a] Formula weight and density include atoms from solvent molecules as specified in the experimental section.

Table V. Fractional Atomic Coordinates for Selected Atoms of Cu(tppb)(pterin) (**1**)[a]

atom	x	y	z
Cu	0.28862 (3)	0.37735 (3)	0.35968 (3)
O4	0.1689 (2)	0.4372 (2)	0.2448 (2)
N1	0.2545 (3)	0.2684 (2)	0.0195 (2)
N2	0.0875 (3)	0.3867 (3)	-0.0708 (2)
N3	0.1243 (2)	0.4152 (2)	0.0863 (2)
N5	0.3663 (2)	0.2745 (2)	0.2688 (2)
N8	0.4252 (3)	0.1576 (3)	0.1140 (3)
N9	0.2050 (2)	0.4959 (2)	0.4277 (2)
N10	0.1976 (2)	0.4500 (2)	0.5433 (2)
N11	0.4267 (2)	0.3566 (2)	0.4498 (2)
N12	0.4024 (2)	0.3367 (2)	0.5616 (2)
N13	0.2257 (2)	0.2216 (2)	0.4968 (2)
N14	0.2440 (2)	0.2186 (2)	0.6013 (2)
C2	0.1593 (3)	0.3537 (3)	0.0141 (2)
C4	0.1927 (3)	0.3876 (3)	0.1710 (2)
C5	0.2994 (3)	0.2990 (3)	0.1814 (2)
C6	0.4631 (3)	0.1890 (3)	0.2803 (3)
C7	0.4896 (3)	0.1336 (3)	0.2004 (3)
C8	0.3251 (3)	0.2416 (3)	0.1042 (3)
C9	0.1202 (3)	0.5308 (3)	0.5762 (3)
C10	0.0771 (3)	0.6299 (3)	0.4827 (3)
C11	0.1327 (2)	0.6059 (2)	0.3897 (2)
C12	0.5005 (3)	0.3266 (3)	0.6121 (3)
C13	0.5888 (3)	0.3411 (3)	0.5331 (3)
C14	0.5394 (3)	0.3609 (2)	0.4312 (2)
C15	0.2413 (3)	0.1064 (3)	0.6803 (3)
C16	0.2192 (4)	0.0347 (3)	0.6279 (3)
C17	0.2090 (3)	0.1091 (3)	0.5134 (3)
B	0.2791 (3)	0.3293 (3)	0.6116 (3)

[a] Numbers in parentheses are the estimated standard deviations in the last figure.

The strong tetragonal field of the copper inner coordination sphere is seen in the long axial Cu–N13 distance (2.218 Å) compared to equatorial Cu–N and Cu–O distances (2.00 Å). Bond distances and angles within the tris(phenylpyrazolyl)hydroborate are unremarkable since they reproduce values previously reported.[8] Variations of the pterin ligand geometry as a function of copper complex composition are considered below.

The six-coordinate complex Cu(ethp)$_2$(phen) (**4**) possesses the tetragonal structure architypal for Jahn–Teller distorted cupric complexes. The inner coordination sphere of **4** consists of four N atoms in the equatorial plane; two N atoms from the phenanthroline ligand and two N atoms from each pteridine ligand, at the typical average distance of 2.03 Å. Pteridine oxygen atoms occupy the axial positions at considerably longer distances of 2.304 Å. The slight distortion from an ideal tetragonal environment again results from the bite requirements of both types of bidentate ligands (phen, 81.5°; ethp, 78.0 and 76.9°). The phenanthroline ligand exhibits a marked N–C and C–C bond distance alternation as previously reported[18] and merits no further discussion. The pteridine ligand geometry does not greatly differ from that observed in the cobalt complexes Co(ethp)$_2$(imidazole)$_2$ and Co(ethp)$_2$(H$_2$O)$_2$.[3] Comments on certain differences are made in the Discussion.

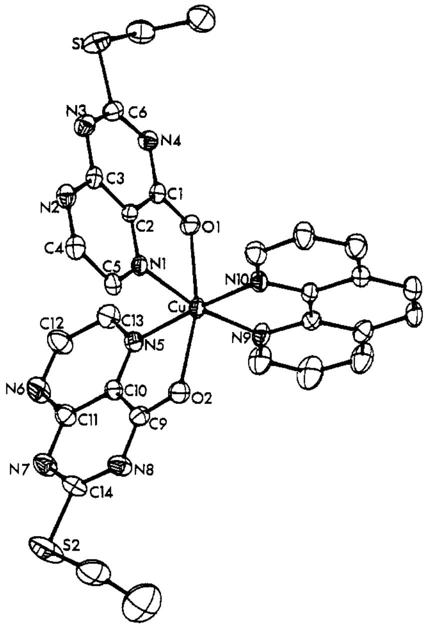

Figure 2. Ortep drawing of Cu(ethp)$_2$(phen) (**4**).

The third structure reported in this paper is of the ionic compound **5**, [Cu(phen)$_2$(acetate)][acetate-H-ethp]. Unlike the previous complexes presented, this compound does not possess a copper-coordinated pteridine, but rather the pteridine molecule appears as part of the anionic counterion. The copper is coordinated by two phenanthroline ligands and one monodentate acetate group in a highly distorted square-pyramidal geometry.

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(18) See ref 19 and see: Fabrietti, A. C.; Franchini, G.; Zannini, P.; Divaira, M. *Inorg. Chim. Acta* **1985**, *105*, 187–191.

Table VI. Fractional Coordinates for Selected Atoms in Cu(ethp)$_2$(phen) (**4**)[a]

atom	*x*	*y*	*z*
Cu	0.23714 (5)	0.26079 (5)	0.23693 (6)
S1	0.5423 (1)	0.3584 (1)	0.7771 (1)
S2	0.3797 (2)	−0.0754 (2)	−0.3778 (2)
O1	0.2646 (2)	0.2567 (3)	0.4368 (3)
O2	0.2478 (3)	0.2288 (3)	0.0238 (3)
N1	0.3896 (3)	0.3053 (3)	0.2770 (3)
N2	0.5920 (3)	0.3792 (3)	0.3634 (4)
N3	0.5593 (3)	0.3688 (3)	0.5586 (4)
N4	0.3920 (3)	0.3052 (3)	0.5945 (3)
N5	0.2980 (3)	0.0938 (3)	0.1567 (3)
N6	0.4026 (4)	−0.1212 (3)	0.0289 (4)
N7	0.3882 (4)	−0.0901 (3)	−0.1598 (4)
N8	0.3049 (4)	0.0879 (3)	−0.1621 (4)
N9	0.0788 (3)	0.2359 (3)	0.2339 (4)
N10	0.1738 (3)	0.4246 (3)	0.2990 (4)
C1	0.3550 (4)	0.2910 (3)	0.4764 (4)
C2	0.4247 (3)	0.3174 (3)	0.3949 (4)
C3	0.5250 (4)	0.3555 (4)	0.4397 (4)
C4	0.5561 (4)	0.3644 (4)	0.2490 (5)
C5	0.4547 (4)	0.3278 (4)	0.2032 (4)
C6	0.4901 (4)	0.3417 (4)	0.6250 (4)
C7	0.4338 (5)	0.3260 (5)	0.8536 (5)
C8	0.3455 (6)	0.4191 (5)	0.9046 (6)
C9	0.2881 (4)	0.1303 (4)	−0.0349 (4)
C10	0.3186 (4)	0.0563 (4)	0.0323 (4)
C11	0.3699 (4)	−0.0522 (4)	−0.0332 (5)
C12	0.3810 (5)	−0.0804 (4)	0.1510 (5)
C13	0.3291 (5)	0.0271 (4)	0.2185 (5)
C14	0.3532 (4)	−0.0187 (4)	−0.2138 (5)
C15	0.3203 (7)	0.0297 (6)	−0.4340 (6)
C16	0.2069 (9)	0.0223 (8)	−0.4656 (9)
C17	0.2236 (4)	0.5171 (4)	0.3336 (5)
C18	0.1685 (4)	0.6259 (4)	0.3807 (6)
C19	0.0596 (4)	0.6370 (4)	0.3929 (6)
C20	0.0028 (4)	0.5399 (4)	0.3570 (5)
C21	−0.1107 (4)	0.5430 (5)	0.3677 (5)
C22	−0.1597 (4)	0.4493 (5)	0.3381 (5)
C23	−0.0986 (4)	0.3396 (4)	0.2901 (5)
C24	−0.1433 (4)	0.2368 (5)	0.2572 (6)
C25	−0.0774 (5)	0.1387 (5)	0.2144 (7)
C26	0.0337 (4)	0.1403 (5)	0.2038 (6)
C27	0.0133 (4)	0.3348 (4)	0.2771 (4)
C28	0.0653 (3)	0.4351 (4)	0.3106 (4)

[a] Numbers in parentheses are the estimated standard deviations in the last figure.

Table VII. Fractional Atomic Coordinates in [Cu(phen)$_2$(acetate)][acetate-H-ethp] (**5**)[a]

atom	*x*	*y*	*z*
Cu	0.13452 (7)	0.21679 (4)	0.08363 (5)
S	0.2354 (2)	0.5989 (1)	0.0525 (1)
O1	0.0966 (4)	0.1261 (2)	0.1255 (3)
O2	0.1839 (4)	0.0863 (3)	0.0385 (3)
O3	0.4095 (4)	0.7445 (2)	−0.1158 (3)
O4	0.3288 (5)	0.8534 (3)	−0.0650 (3)
O5	0.4255 (7)	0.9162 (4)	−0.1297 (5)
N1	0.0888 (4)	0.2919 (3)	0.1696 (3)
N2	0.2928 (4)	0.2207 (3)	0.1835 (3)
N3	−0.0220 (4)	0.2187 (3)	−0.0166 (3)
N4	0.1824 (4)	0.2857 (3)	0.0057 (3)
N5	0.4669 (4)	0.6328 (3)	−0.2012 (3)
N6	0.3986 (5)	0.4988 (3)	−0.1657 (4)
N7	0.3228 (5)	0.5468 (3)	−0.0638 (3)
N8	0.3278 (4)	0.6711 (3)	−0.0416 (3)
C1	0.3903 (5)	0.1843 (3)	0.1897 (4)
C2	0.4921 (5)	0.1825 (3)	0.2649 (4)
C3	0.4926 (5)	0.2200 (4)	0.3363 (4)
C4	0.3912 (5)	0.2603 (3)	0.3311 (4)
C5	0.2912 (5)	0.2598 (3)	0.2533 (3)
C6	0.1837 (5)	0.2981 (3)	0.2453 (3)
C7	−0.0121 (6)	0.3260 (4)	0.1621 (4)
C8	−0.0218 (6)	0.3688 (4)	0.2290 (5)
C9	0.0711 (6)	0.3738 (4)	0.3055 (4)
C10	0.1792 (5)	0.3386 (3)	0.3158 (4)
C11	0.2842 (6)	0.3394 (4)	0.3949 (4)
C12	0.3838 (6)	0.3022 (4)	0.4023 (4)
C13	−0.1239 (6)	0.1838 (4)	−0.0249 (4)
C14	−0.2263 (5)	0.1891 (4)	−0.1002 (5)
C15	−0.2239 (6)	0.2296 (4)	−0.1687 (4)
C16	−0.1187 (5)	0.2671 (3)	−0.1607 (4)
C17	−0.0200 (5)	0.2604 (3)	−0.0833 (4)
C18	0.0908 (5)	0.2967 (3)	−0.0712 (3)
C19	0.2863 (5)	0.3192 (3)	0.0193 (4)
C20	0.3037 (5)	0.3642 (4)	−0.0439 (4)
C21	0.2121 (6)	0.3753 (3)	−0.1213 (4)
C22	0.1022 (5)	0.3405 (3)	−0.1368 (4)
C23	−0.0012 (6)	0.3468 (4)	−0.2158 (4)
C24	−0.1065 (6)	0.3123 (4)	−0.2273 (4)
C25	0.1161 (8)	0.0040 (4)	0.1194 (5)
C26	0.1344 (6)	0.0761 (3)	0.0914 (4)
C27	0.3760 (5)	0.5576 (4)	−0.1253 (4)
C28	0.4524 (6)	0.5098 (4)	−0.2224 (5)
C29	0.4869 (6)	0.5758 (4)	−0.2401 (4)
C30	0.4109 (5)	0.6239 (3)	−0.1441 (4)
C31	0.3824 (5)	0.6843 (3)	−0.0997 (4)
C32	0.3032 (5)	0.6040 (3)	−0.0282 (4)
C33	0.2132 (7)	0.5066 (4)	0.0596 (5)
C34	0.165 (1)	0.4903 (6)	0.1272 (7)
C35	0.3604 (8)	0.9152 (5)	−0.0899 (6)
C36	0.317 (1)	0.9728 (5)	−0.0649 (9)

[a] Numbers in parentheses are the estimated standard deviations in the last figure.

The square base is defined by N3 and N4 of one phenanthroline, N2 from the other phenanthroline, and O1 of the acetate ligand. Bond distances within this base are in the range 1.97–2.04 Å. The remaining phenanthroline donor atom, N1, occupies the axial site at a longer distance of 2.200 Å. Approximately trans to this axial nitrogen is the second oxygen atom (O2) of acetate at an essentially nonbonded distance of 2.717 Å. Figure 3a shows a view of this cation that emphasizes the pseudo-square-pyramidal structure. The structure of **5** is not identical with any previously reported structures of the [Cu(phen)$_2$(acetate)] cation but most closely resembles the salt [Cu(phen)$_2$(acetate)][BF$_4$].[19] The interesting feature of **5** from the perspective of this paper is the presence of ethp in the crystal structure as part of the counteranion for the copper cation rather than as a ligand for Cu(II). Figure 3b shows a view of the anion wherein the enol tautomer of ethp hydrogen bonds through O4 to a second acetate ion resulting in the formation of the anionic unit [acetate-H-ethp$^-$]. The distances of the ethp portion are nearly identical (within experimental error) to the corresponding bonds in Cu(ethp)$_2$(phen), with one exception. Distance N7–C32 (1.294 Å) is significantly shorter in the [acetate-H-ethp$^-$] anion than in Cu(ethp)$_2$(phen) (average C–N = 1.322 Å). In the acetate moiety, the C–O bond involved in hydrogen bonding is longer than the second C–O distance, 1.34 vs 1.16 Å. These two observations indicate that the unit of negative charge seems to be delocalized over one acetate oxygen and the pyrimidine ring in ethp. The packing of ions in the unit cell of crystalline **5** is shown in Figure 4.

Discussion

We have previously documented the variety of bidentate pteridine and pterin ligands that readily form cobalt and molybdenum complexes.[3] This paper describes the extension of our syntheses to the biologically relevant metals iron and copper and to other divalent first-row metals. While the focus of our work reported here is copper–pteridine chemistry, complexes of the other metals were studied to demonstrate the generality of the methods. The distinguishing features of our results are as follows: (a) nonaqueous preparations; (b) isolation of ternary metal-pterin complexes by selecting a suitable ancillary ligand; (c) structural determinations for cupric complexes illustrating the effects of bis, mono, and *no* pteridine coordination. In addition to these features, the stacking interaction between pterin and a phenyl ring in Cu(tppb)(pterin) suggests how the pterin cofactor in PAH might

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(19) Clifford, F.; Counihan, E.; Fitzgerald, W.; Seff, K.; Simmons, C.; Tyagi, S.; Hathaway, B. J. *J. Chem. Soc., Chem. Commun.* **1982**, 196.

Table VIII. Selected Bond Distances and Angles in Copper Pterinate Structures[a]

Cu(tppb)(pterin) (**1**)		Cu(ethp)$_2$(phen) (**4**)		[Cu(phen)$_2$(acetate)]$^+$-[acetate-H-ethp]$^-$ (**5**)	
		Interatomic Distances (Å)			
Cu–O4	1.968 (2)	Cu–N1	2.017 (4)	Cu–N1	2.200 (5)
Cu–N5	2.033 (3)	Cu–N5	2.061 (3)	Cu–N2	2.004 (4)
Cu–N9	1.986 (3)	Cu–N9	2.021 (4)	Cu–N3	1.992 (4)
Cu–N11	2.019 (3)	Cu–N10	2.031 (4)	Cu–N4	2.041 (5)
Cu–N13	2.218 (2)	Cu–O1	2.303 (4)	Cu–O1	1.969 (4)
O4–C4	1.282 (4)	Cu–O2	2.305 (4)	Cu–O2	2.717 (5)
N1–C2	1.333 (4)	C1–C2	1.449 (7)	C26–O1	1.261 (8)
N1–C8	1.337 (5)	C1–N4	1.349 (6)	C26–O2	1.21 (1)
N2–C2	1.334 (5)	C1–O1	1.250 (5)	C27–C30	1.397 (9)
N3–C2	1.378 (5)	C2–C3	1.390 (6)	C27–N6	1.373 (9)
N3–C4	1.318 (4)	C2–N1	1.347 (6)	C27–N7	1.37 (1)
N5–C5	1.343 (4)	C3–N2	1.362 (7)	C28–C29	1.38 (1)
N5–C6	1.337 (4)	C3–N3	1.351 (7)	C28–N6	1.31 (1)
N8–C7	1.315 (6)	C4–C5	1.398 (7)	C29–N5	1.320 (9)
N8–C8	1.357 (4)	C4–N2	1.305 (7)	C30–C31	1.460 (9)
C4–C5	1.441 (4)	C5–N1	1.318 (7)	C30–N5	1.33 (1)
C5–C8	1.390 (5)	C6–N3	1.325 (7)	C31–N8	1.342 (9)
C6–C7	1.402 (6)	C6–N4	1.335 (6)	C31–O3	1.244 (8)
				C32–N7	1.294 (9)
				C32–N8	1.347 (8)
				C33–C34	1.44 (2)
				C35–C36	1.33 (2)
				C35–O4	1.34 (1)
				O3–O4	2.540 (9)
		Interatomic Angles (deg)			
O4–Cu–N5	83.10 (9)	N1–Cu–N5	89.5 (1)	N1–Cu–N2	79.6 (2)
O4–Cu–N9	90.26 (9)	N1–Cu–N9	168.5 (1)	N1–Cu–N3	98.7 (2)
O4–Cu–N11	164.71 (8)	N1–Cu–N1	92.1 (1)	N1–Cu–N4	99.2 (2)
O4–Cu–N13	103.09 (9)	N1–Cu–O1	78.0 (1)	N1–Cu–O1	102.5 (2)
N5–Cu–N9	171.93 (8)	N1–Cu–O2	94.4 (1)	N2–Cu–N3	176.8 (2)
C2–N1–C8	115.6 (3)	N5–Cu–N9	97.8 (1)	N2–Cu–N4	96.0 (2)
N5–Cu–N11	98.1 (1)	N5–Cu–N10	174.6 (2)	N2–Cu–O1	90.5 (2)
N5–Cu–N13	93.92 (9)	N5–Cu–O1	89.9 (1)	N3–Cu–N4	81.5 (2)
N9–Cu–N11	87.1 (1)	N5–Cu–O2	76.9 (1)	N3–Cu–O1	92.6 (2)
N9–Cu–N13	92.05 (9)	N9–Cu–N10	81.5 (1)	N4–Cu–O1	158.2 (2)
N11–Cu–N13	92.05 (9)	N9–Cu–O1	93.1 (2)	Cu–O1–C26	110.7 (4)
Cu–O4–C4	112.8 (2)	N9–Cu–O2	96.0 (2)	C25–C26–O1	116.9 (7)
Cu–N5–C5	109.1 (2)	N10–Cu–O1	95.5 (1)	C25–C26–O2	121.5 (7)
Cu–N5–C6	134.4 (2)	N10–Cu–O2	97.8 (1)	O1–C26–O2	121.6 (6)
Cu–N9–C11	135.6 (2)	O1–Cu–O2	164.8 (1)	C30–C31–N8	116.9 (6)
Cu–N9–N10	115.2 (2)	Cu–N1–C5	127.3 (3)	C30–C31–O3	120.2 (6)
Cu–N11–N12	114.6 (2)	Cu–N5–C10	114.7 (3)	N8–C31–O3	122.9 (6)
Cu–N11–C14	138.1 (2)	Cu–N5–C13	126.3 (3)	C36–C35–O4	117 (1)
Cu–N13–N14	111.3 (2)	Cu–N9–C26	129.3 (3)		
Cu–N13–C17	138.4 (2)	Cu–N9–C27	112.5 (3)		
		Cu–N10–C17	129.5 (3)		
		Cu–N10–C28	112.2 (3)		
		Cu–O1–C1	108.1 (3)		
		Cu–O2–C9	109.2 (3)		

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

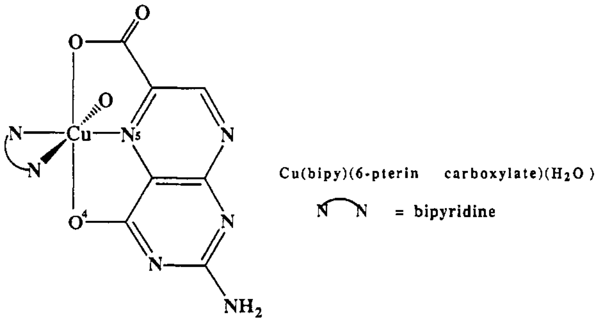
Table IX. Comparison of Bond Distances (Å) in Cu(bpy)(PC)(H_2O), Cu(tppb)(pterin), and Cu(ethp)$_2$(phen)

bond	Cu(bpy)(PC)(H_2O)	Cu(ethp)$_2$(phen)	Cu(tppb)(pterin)
Cu–O4	2.499	2.303	1.968
C4–O4[a]	1.238	1.250	1.282
C4–N3	1.339	1.349	1.318
C2–N3	1.359	1.335	1.378
C2–N1	1.361	1.325	1.333

[a] The atom numbers for the pyrimidine ring correspond to those shown in the resonance scheme given in the Discussion.

also serve to orient the phenylalanine substrate.

Our work is complemented by other recent reports of metal complexation by pterins and the flavin analogue lumazine. The only other copper pterin structure reported is for Cu(PC)(bpy)(H_2O) [PC = 6-pterincarboxylate] reported by Yamauchi et al.[20] Data from our results considered with those for Cu(bpy)(PC)(L) provide the opportunity to identify trends in coordination modes, bond variations and physical properties.



As found in our structures, atoms O4/N5 of the pterin carboxylate (PC) chelate the metal in Cu(PC)(bpy)(H_2O). The resulting coordination sphere is most similar to Cu(ethp)$_2$(phen) (**4**). These complexes both display an equatorial plane occupied by two nitrogen atoms from the ancillary ligand (phen or bpy) and the N5

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(20) Kohzuma, T.; Masuda, H.; Yamauchi, O. *J. Am. Chem. Soc.* **1989**, *111*, 3431–3433.

atom of pterin or ethp. Two weak axial bonds to formally anionic oxygen atoms of the pteridine complete the coordination sphere. In contrast, the Cu^{II}–pterin interactions in Cu(PC)(bpy)(H_2O) are significantly different from those in Cu(tppb)(pterin). Both pterin and PC bind through the O4/N5 donor atoms, but the Cu–O4 distance in Cu(PC)(bpy)(H_2O) is considerably longer than this bond in Cu(tppb)(pterin) (2.499 vs 2.033 Å). We feel this striking difference is due to the relative orientation of the pterin ligands within the coordination sphere of these complexes. The pterin plane lies within the equatorial plane in Cu(tppb)(pterin) in contrast to the axial alignment of PC in Cu(PC)(bpy)(H_2O). As a result the pterin contributes to the strong field in the equatorial plane of Cu(tppb)(pterin) while PC participates in weaker axial interactions in Cu(PC)(bpy)(H_2O). Though both pterin ligands are formally anionic, the Cu–O bond strength affects the electronic distribution within the pyrimidine ring portion of pterin, as reflected by different C–N bond distances. Pterin deprotonation redistributes electron density in the pyrimidine ring, as is schematically described below.

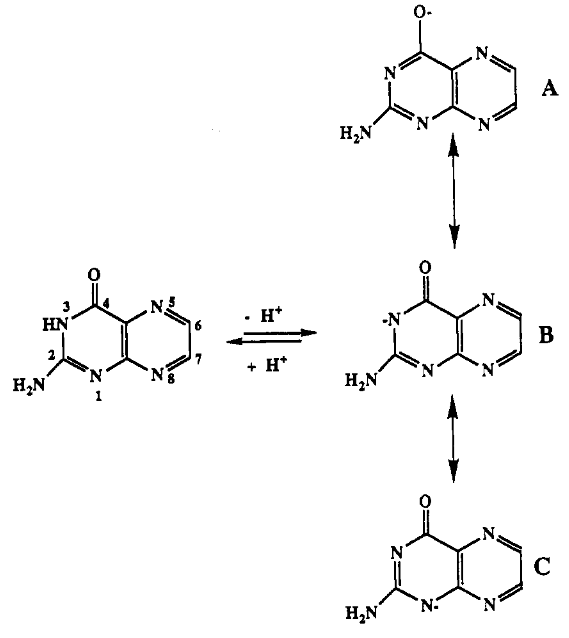

Table IX shows the relevant Cu–O, C–O, C–N distances in the pyrimidine ring for the cupric pterin complexes. A smooth trend exists where a decrease in Cu–O bond length parallels a longer C–O distance. Inspection of the pyrimidine C–N bond distances in each complex suggests which resonance structure best describes the electronic distribution in the anionic pterin. The complex with the strongest Cu–O4 interaction, Cu(tppb)(pterin), has resonance structure A characterized by a short N3–C4 distance. The complex with the weakest Cu–O4 interaction, Cu(bpy)(PC)(H_2O), appears to prefer resonance form C, distinguished by a long N1–C2 distance. Complex Cu(ethp)$_2$(phen) has two short C–N distances indicating that resonance forms B and C combine to delocalize the negative charge over the region N1–C2–N3. In contrast to significant differences in the pyrimidine bond distances, the pyrazine ring of the pteridine system in all three complexes is essentially the same.

The EPR parameters observed for our cupric pteridine complexes and for Cu(PC)(bpy)(L) are surprisely insensitive to differences in the copper coordination sphere. All complexes have values of $g_\parallel$ and $g_\perp$ close to those obtained from the cupric ion in phenylalanine hydroxylase. The copper hyperfine tensor A shows slightly more variation and the values for the Cu–pterin model complexes bracket the value of $A_\parallel$ observed in PAH. We note within the data in Table III a correlation of $A_\parallel$ with pterin orientation relative to the equatorial plane. Large values of $A_\parallel$ correspond to complexes having perpendicular pterin ligands (cf., 171.5, 169, 181 G) and the smaller values of $A_\parallel$ correspond to complexes with equatorally bound pterin (cf., 158 and 162 G). Smaller values of $A_\parallel$ might be caused by delocalization of unpaired spin density onto the pterin ligand. X-ray crystallography gives evidence for stronger Cu–pterin interactions when the pterin is equatorial. Likewise, electronic spectral data suggest increased metal–pterin interactions as judged by larger bathochromic shifts in pterin UV absorptions (see results). Given the complexity of the factors that combine to determine the copper hyperfine value,[21] it is probably not valid to infer much about the copper environment in PAH by using $A_\parallel$ as a primary criterion. However, the data is consistent with a previous postulation that the cupric site of PAH has two nitrogen donor atoms in addition to the N5 of biopterin.

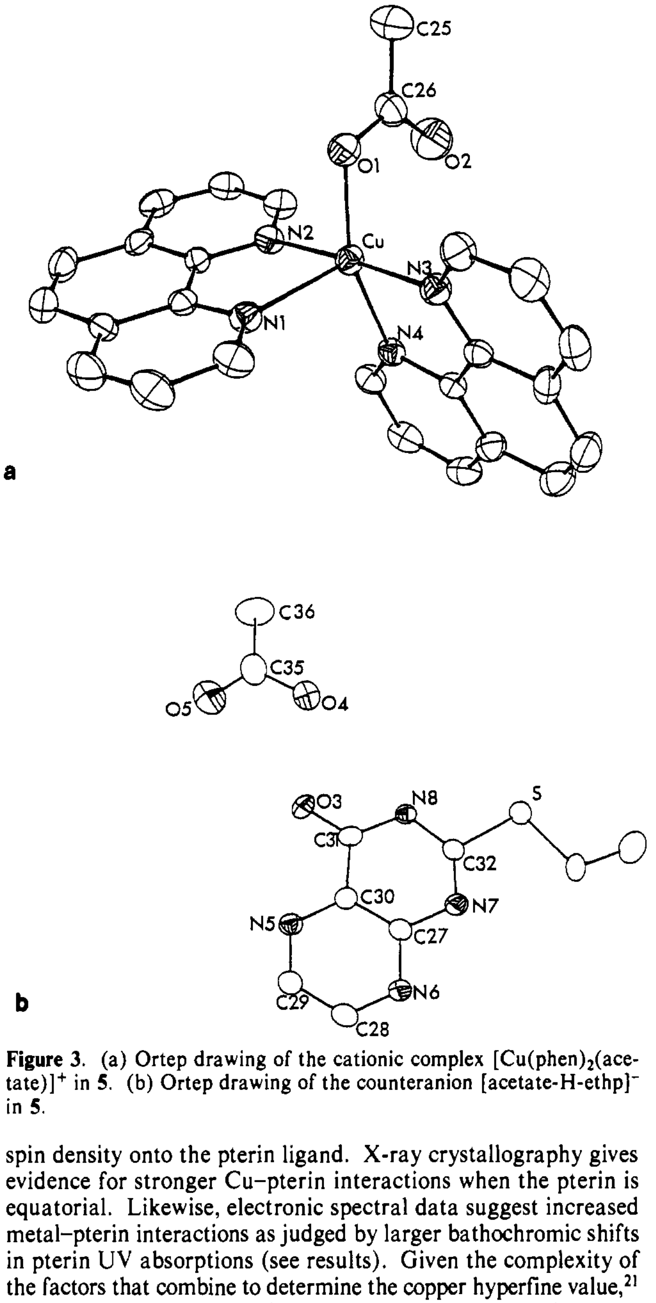

Figure 3. (a) Ortep drawing of the cationic complex [Cu(phen)$_2$(acetate)]$^+$ in **5**. (b) Ortep drawing of the counteranion [acetate-H-ethp]$^-$ in **5**.

The spectroscopic and magnetic susceptibility measurements made for all first-row metal complexes point to a moderate ligand field strength for the pterinate ligand and to structural homology among different metals. The greater bathochromic shifts for pterin-based UV absorptions of M(tppb)(pteridinate) (M = Co, Ni, and Cu but *not* Zn) as compared to M(pteridinate)$_2$(L)$_2$ [L_2 = phen, (H_2O)$_2$ or (imidazole)$_2$^{3c}] suggest increased metal–pteridine interactions. Since the electron-deficient pteridine can serve as a π-acceptor ligand, the above observation is consistent with increased back-bonding in those complexes having a single pteridine. Pterinate orientation may also play a role in varying back-bonding in five-coordinate complexes. However, the six-coordinate complexes Co(ethp)$_2$(H_2O)$_2$ and Co(ethp)$_2$(imidazole)$_2$ have nearly identical electronic spectra and Co–O4 bond distances even though the two ethp ligands are coplanar in the former complex and orthogonal in the latter complex.[3c] Last, we note

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[21] Gewirth, A.; Cohen, S.; Schugar, H. J.; Solomon, E. I. *Inorg. Chem.* **1987**, *26*, 1133.

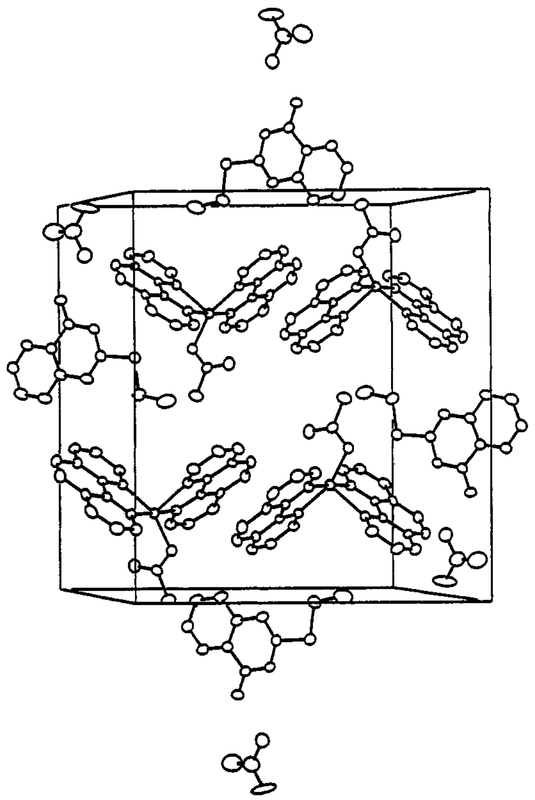
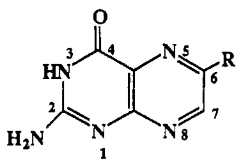


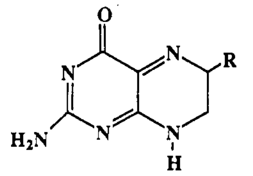
Figure 4. Unit cell drawing showing the packing of ions in [Cu(phen)$_2$(acetate)]$^+$[acetate-H-ethp]$^-$ (**5**). The view is down the *b* axis.

that the unusual charge-transfer absorption present only in the ferrous complexes may be useful in identifying such interactions in the enzyme.[22] At this date no evidence exists to support the coordination of pterin to Fe^{II} in PAH.

The natural pterin cofactor for PAH, tetrahydrobiopterin, is active in the fully reduced state.[2] Tetrahydrobiopterin is known to undergo oxidation to the thermodynamically unstable but electrochemically reversible quinonoid dihydropterin. No evidence exists for participation of fully oxidized pterin during enzyme turnover. However, the importance of our results and those of Yamauchi et al. concerning cupric pterin complexes is related to the similarity of the O4/N5 binding site in oxidized pterin to the potential binding site in the quinonoid form of dihydropterin.



oxidized pterin



quinonoid dihydropterin

The role of reduced tetrahydropterin combined with cupric complexes is currently under investigation in our group. Preliminary results of experiments where tetrahydropterin is added to [Cu(tppb)(dmf)$_2$][ClO$_4$] indicate a redox reaction occurs that produces an intermediate of intensely blue color (λ_{max} = 608 nm).[23] The energy of this strong absorption is dependent on the type of copper complex used in the reduction, suggesting that the transient species contains copper and the ancillary nitrogen-donor ligand in addition to a reduced form of pterin. Ultimately copper(II) is reduced to Cu(I), but the fate of the pterin is not yet known. Further study of this reaction is in progress.

In summary, we have demonstrated the generality of our synthetic procedures for metal(II) pterinate complexes. Spectroscopic and magnetic measurements indicate a moderate ligand field strength for deprotonated pteridines bound to first-row divalent metal ions. The crystal structures of **1** and **4** make significant contributions to the meager structural data available for pterins complexed to copper(II). EPR parameters for all known copper pteridine complexes were compared. In contrast to the uniform *g* values observed for copper pteridine complexes of diverse structure, only the copper hyperfine constant $A_{\parallel}$ is sensitive to changes in the copper environment. Spectroscopic and structural data indicate a stronger metal–pteridine interaction when the pteridine is equatorially bound. These data provide a good starting point for continued development of Cu(II)–pterin model systems.

Acknowledgment. We are grateful for financial support from the National Institutes of Health, (Grant GM42049-01), Exxon Education Foundation, and Bryn Mawr College.

Supplementary Material Available: Listings of final positional parameters for all non-hydrogen atoms and calculated positions of hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, and intramolecular bond angles and bond distances and Ortep drawings of the unit cells for Cu(tppb)(pterin) (**1**) and Cu(ethp)$_2$(phen) (**4**) (39 pages); listings of observed and calculated structure factors (79 pages). Ordering information is given on any current masthead page.

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(22) Previous work concerning pteridine coordination on Ru(II) has also identified a strong charge-transfer absorption in the visible spectral region: (a) Abelleira, A.; Galang, R.; Clarke, M. J. *Inorg. Chem.* **1990**, *29*, 633–639. (b) Bessenbacher, C.; Vogler, C.; Kaim, W. *Inorg. Chem.* **1989**, *28*, 4645–4648.

(23) In a typical experiment, a methanolic solution of 6,7-dimethyltetrahydropterin is added via syringe to a methanolic solution of the copper complex. Immediately an intense blue color appears, fading to a colorless solution within 10 min. At higher concentrations, a white precipitate forms that is identified as CuClO$_4$ by infrared spectroscopy. If the reaction is performed in DMF, no blue intermediate is observed.