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Synthesis, crystal structure and properties of a new binuclear iron(III) complex as a model for the purple acid phosphatases*

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Abstract

The new binucleating ligand 2,6-bis[(2-hydroxybenzyl)(2-pyridylmethyl)-amino-methyl]-4-methylphenol, (H_3BBPMP), has been prepared. The reaction of H_3BBPMP with $Fe(ClO_4)_2 \cdot 6H_2O$ in the presence of sodium acetate in methanolic solution affords the title complex, $[Fe_2(BBPMP)(OAc)_2]ClO_4 \cdot H_2O$ (**1**). The crystal structure of **1** has been determined by X-ray crystallography. Crystal data: monoclinic, space group $P2_1/n$, $a = 14.863(5)$, $b = 12.315(3)$, $c = 20.872(8)$ Å, $\beta = 90.83(3)°$, $Z = 4$. Electrochemical, magnetic and electronic structural as well as Mossbauer spectral properties of **1** have been investigated. Some of these properties indicate that complex **1** represents an interesting model for the purple acid phosphatase active site.

It is well established that binuclear iron centers have important functional roles in the active sites of iron proteins such as hemerythrin (Hr) [1], ribonucleotide reductase (RR) [2], methane monooxygenase (MMO) [3] and purple acid phosphatases (PAPs) [4]. While hemerythrin is the prototype and best characterized member of this class of proteins, the coordination chemistry, magnetic, spectroscopic and electrochemical properties of PAPs are yet less well understood [5]. They constitute a novel class of metalloenzymes involved in regulation of the levels of phosphate and phosphorylated metabolites in a wide range of organisms [6]. However, to date, only enzymes isolated from bovine spleen and porcine uterus (also referred to as 'uteroferrin') have been examined in some detail. The active site of these PAPs consists of a dinuclear iron center with two accessible oxidation states – a catalytically inactive, purple Fe(III)–Fe(III) form characterized by typical absorption maxima at $\lambda_{max} = 550$ nm, and an enzymatically active, pink Fe(III)–Fe(II) form which is blue shifted (λ_{max} 505 nm) [4]. These bands are assigned as being tyrosinate-to-iron(III) charge transfer transitions [4]. Resonance Raman spectra of the purple and pink forms, using visible excitation, confirm the presence of tyrosine ring modes [7]. In both oxidation states, the irons are antiferromagnetically coupled, giving rise to $S = 0$ and $S = 1/2$ ground states, respectively [6]. The quantitative interconversion of the two forms and the similar extinction coefficients found in both states, indicate that tyrosine binds only to the iron center that remains trivalent [6, 7]. The presence of histidine imidazole is a probable ligand to both iron centers, as has been demonstrated by NMR [8] and ENDOR [9] studies.

In the past few years, a large number of binuclear iron complexes as models for Hr, RR, MMO and PAPs have been reported [1–6]. However, most of these complexes do not exhibit the characteristic spectral properties observed in purple acid phosphatases [10]. From the coordination environment proposed for PAPs [6, 8], it seems obvious that the presence of at least one phenolate group as a terminal ligand is required to obtain suitable biomimetic complexes. Moreover, the stabilization of such complexes in the mixed-valence (Fe^{II}–Fe^{III}) and oxidized (Fe_2^{III}) forms displaying reversible redox properties appears to be essential to the biological activity of these metalloproteins. Electrochemical studies using coulometric methods show that the redox potentials for uteroferrin are 0.367 V at pH = 5.0 and 0.306 V at pH = 6.0 versus a normal hydrogen electrode [11]. Therefore, the synthesis and characterization of new, binuclear iron complexes with relevant N,O-donor ligands (phenolate, imidazole and pyridine) is an important area of investigation. Very recently, we reported the synthesis and physicochemical

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*Dedicated to Professor Karl Wieghardt on the occasion of his 50th birthday

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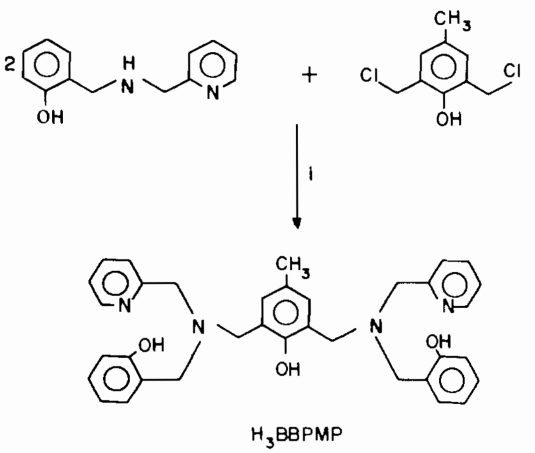
properties of the $[Fe_2^{III}(BBPPNOL)(OAc)_2]^+$ complex[*] as a potential model for the visible chromophore of PAPs [12]. Unfortunately, crystals suitable for X-ray diffraction studies of this species have not been obtained.

In this work, we describe the preparation, structure characterization, electrochemical and spectral properties of a binuclear iron complex, with a new N_4O_3-donor binucleating ligand (H_3BBPMP) which contains phenolate and pyridine as pendant arms.

Experimental

Syntheses

The ligand 2,6-bis[(2-hydroxybenzyl)(2-pyridylmethyl)-amino-methyl]-4-methylphenol (H_3BBPMP) was prepared in good yield by nucleophilic substitution of 2,6-bis(chloromethyl)-4-methylphenol [13] with (2-hydroxybenzyl)(2-pyridylmethyl)amine (HBPA)[**] by the route in Scheme 1: yield 50%; m.p. = 167 °C. The $[Fe_2^{III}(BBPMP)(OAc)_2]ClO_4 \cdot H_2O$ complex was prepared as follows. To a methanolic solution of $Fe(ClO_4)_2 \cdot 6H_2O$ was added sodium acetate, Et_3N and H_3BBPMP. The clear deep blue solution was heated to 40 °C and stirred for 10 min. After cooling the solution to room temperature, a blue microcrystalline precipitate was formed, which was filtered off, and washed with isopropanol and ether. Single crystals suitable for X-ray crystallography were obtained by recrystallization from a 2-propanol-acetone (1:1) solution of **1**. **Caution**: As with all perchlorate salts, samples should be handled with care.



Scheme 1 Synthesis of the ligand H_3BBPMP: reagents and conditions: i, thf, Et_3N, argon.

Results and discussion

All new compounds gave satisfactory elemental analysis (C, H, N). The molecular structure[†] and atomic numbering scheme of **1** are illustrated in Fig. 1. No crystallographic symmetry is imposed on the cation, resulting in the observation of distinct ferric sites in the complex cation. The molecule consists of two six-coordinate iron atoms tribridged by one phenolate group and two carboxylate ligands. The nitrogen (amine and pyridyl) and oxygen (phenolate) donors of the ligand $BBPMP^{3-}$ complete the octahedral environment of the two iron centers in a facial terminal arrangement. Interestingly, the two terminal phenolate oxygen donor atoms coordinate *trans* to the bridging phenolate group. This result contrasts with that observed in the closely related $[LCo_2(OPr)_2]^+$ complex [14] with a similar NO-donor set, in which two pyridyl groups are *trans* rather than *cis* to the bridging phenolate. The Fe(1)–O(1) and Fe(2)–O(1) bond distances (av. 2.055(8) Å) in **1** are significantly longer than the corresponding Fe(III)–O(phenolate) bond lengths observed in the mixed-valence $[Fe^{II}Fe^{III}(BIMP)(\mu\text{-}OBz)_2]^{2+}$ (1.958(2) Å) [15] and $[Fe^{II}Fe^{III}(BPMP)(\mu\text{-}OPr)_2]^{2+}$ (1.943(2) Å) [13] complexes and is a reflection of the short terminal Fe(1)–O(2) and Fe(2)–O(3) bond lengths (av. 1.855(8) Å) which are coordinated in *trans* positions to the bridged phenolate group. It is important to note that the Fe(1)–O(1)–Fe(2) bridging angle is 118.3(4)° which is somewhat larger than the 115.7(8) and 113.1(1)° values observed for the $BIMP^-$ and $BPMP^-$ complexes, respectively [13, 15]. Consequently, the Fe...Fe distance of 3.528(8) Å for **1** is larger than in the $BIMP^-$ and $BPMP^-$ complexes (3.426(2) and 3.365(1) Å, respectively) [13, 15]. In addition, it is worth noting that **1** represents a rare example of binuclear Fe(III) complexes

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[*] Abbreviations. $H_3BBPPNOL$, *N,N′,N,N′*-bis[(2-hydroxybenzyl)(2-pyridylmethyl)]-2-ol-1,3-propanediamine; HBPMP, 2,6-bis[(bis(2-pyridylmethyl)amino)-methyl]-4-methylphenol, HBIMP, 2,6-bis[(bis(1-methylimidazol-2-ylmethyl)amino)-methyl]-4-methylphenol; H_3BBPPM, 2,6-bis[(2-hydroxybenzyl)(2-pyridylmethyl)-amino-methyl]-4-methylphenol; H_3L, 2,6-bis-bis{[(2-hydroxyphenyl)(2-pyridylmethyl)amino]methyl}-4-methylphenol; OAc, acetate, OPr, propionate, OBz, benzoate

[**] HBPA was obtained from a condensation reaction of 2-(aminomethyl) pyridine and salicylaldehyde followed by reduction with $NaBH_4$ in methanol.

[†] Crystal data for **1**: $[Fe_2(BBPMP)(OAc)_2]ClO_4$ H_2O, $M = 950.99$, monoclinic, $P2_1/n$, (C_{2h}^5; No. 14), $a = 14.863(5)$, $b = 12\ 315(3)$, $c = 20\ 872(8)$ Å, $\beta = 90.83(3)°$, $V = 3820\ 0$ Å^3, $Z = 4$, $D_c = 1.65$ g cm^{-3}. Crystal dimensions $0\ 42 \times 0.25 \times 0.12$ mm; Cu Kα (1.540562 Å); $T = 298$ K. CAD-4 Enraf-Nonius diffractometer. Data were reduced using the SDP program package and the structure was solved and refined with the SHELX-76 program package. Absorption correction with DIFABS of SDP program package was applied, with max and min. transmission factors of 1.619 and 0 651. Hydrogen atoms were included at calculated positions with fixed U values (isotropic thermal parameters) of 0.05 Å^2, $\mu = 21.3$ cm^{-1}; $2 < \theta < 54\ 9°$, 4393 unique reflections; 1857 with $I > 3\sigma(I)$, 510 least-squares parameters, $R = 0.0752$ ($R_w = 0.0784$).

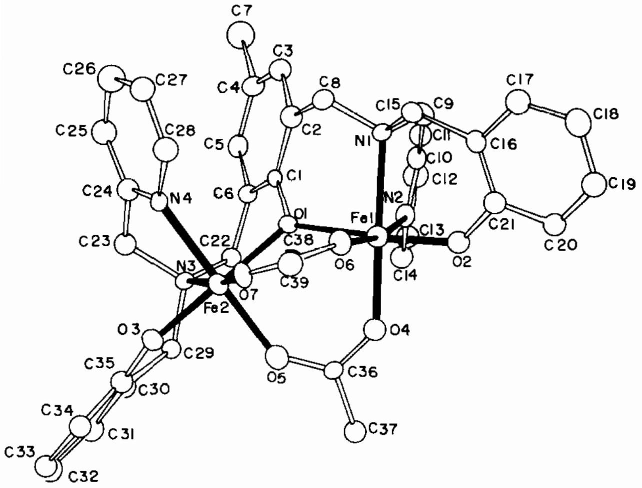

Fig. 1. X-ray structure of cations in crystals of **1**. Selected bond lengths (Å) and angles (°). O1–Fe1 2.054(8), O2–Fe1 1.850(8), O4–Fe1 1.966(8), O6–Fe1 1.980(8), N1–Fe1 2 18(1), N2–Fe1 2.14(1), O1–Fe2 2.056(8), O3–Fe2 1.861(8), O5–Fe2 1.994(8), O7–Fe2 1.954(8), N3–Fe2 2.17(1), N4–Fe2 2.13(1), O2–Fe1–O1 176.2(3), O4–Fe1–O1 91.1(3), O4–Fe1–O2 92.6(4), O6–Fe1–O1 88.8(4), O6–Fe1–O2 91.7(4), O6–Fe1–O4 97.7(4), N1–Fe1–O1 87.7(3), N1–Fe1–O2 88.5(4), N1–Fe1–O4 169.3(4), N1–Fe1–O6 92.8(4), N2–Fe1–O1 85.6(4), N2–Fe1–O2 93.4(4), N2–Fe1–O4 90.4(4), N2–Fe1–O6 170.2(4), N2–Fe1–N1 78.9(4), O3–Fe2–O1 175.2(4), O5–Fe2–O1 86.5(3), O5–Fe2–O3 93 3(4), O7–Fe2–O1 91.8(3), O7–Fe2–O3 93.0(4), O7–Fe2–O5 97.9(4), N3–Fe2–O1 87.0(3), N3–Fe2–O3 88.2(4), N3–Fe2–O5 89 8(4), N3–Fe2–O7 172.2(4), N4–Fe2–O1 85 2(4), N4–Fe2–O3 93 9(4), N4–Fe2–O5 165.5(4), N4–Fe2–O7 94.3(4), N4–Fe2–N3 77 9(4), Fe.. Fe 3.528(8), Fe1–O1–Fe2 118.3(4).

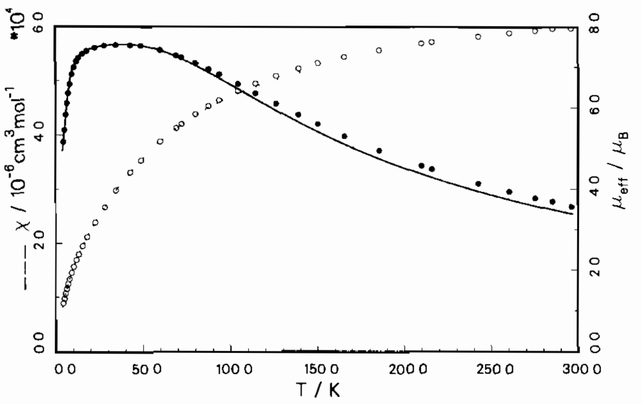

Fig. 2 Magnetic susceptibility of **1** as function of temperature (○. experimental data) and temperature dependence of the effective magnetic moment of **1** (○: experimental data).

containing the (μ-phenolate)(μ-OAc)$_2$ structural entity which have been crystallographically characterized [16].

The variable temperature magnetic data for a solid sample of **1** collected in the temperature range of 4.5 to 296.2 K indicate that the iron ions are weakly coupled antiferromagnetically (Fig. 2). The data were fitted by using the expression for molar susceptibility versus temperature from the spin-exchange Hamiltonian $\mathscr{H} = -2JS_1\cdot S_2$ ($S_1=S_2=5/2$) [17] and the following parameters: $g=2.00$ (fixed); $J=-6.0$ (± 1) cm^{-1}; % imp. = 1.7 (± 0.1)%; $\theta = -1.5$ K. The temperature independent paramagnetism ($TIP = 400\times 10^{-6}$ cm^3/mol) was also taken into account. The J value of -6.0 cm^{-1} lies in the lower end of the range of values found for (μ-alkoxo)(μ-O$_2$CR)$_2$ [12, 18], (μ-hydroxo)(μ-O$_2$CR)$_2$ [19] and (μ-phenolate)(μ-O$_2$CR)$_2$ [16, 20] tribridged binuclear Fe(III) complexes.

The ^{57}Fe Mössbauer spectrum of **1** at 115 K consists of a single quadrupole doublet with an isomer shift $\delta = 0.46 \pm 0.02$) mm/s (referred to metallic iron at room temperature) and a quadrupole splitting $\Delta E_Q = 1.093 \pm 0.002$ mm/s. These parameters are typical of high-spin Fe(III) ions [21] in agreement with the magnetic susceptibility data of **1**, and are also comparable to those observed for the oxidized form of PAPs [7] and the analogous model complex [Fe$_2^{III}$(BBPPNOL)(μ-OAc)$_2$]$^+$ [12] for which two doublets of equal area have been detected. These observations, together with the X-ray crystal structure of **1** (Fig. 1), clearly show that the Mössbauer spectrum is not affected by the small differences in the coordination environment of the two iron sites in **1**. Therefore, these data support the low symmetric structures proposed for PAPs and [Fe$_2^{III}$(BBPPNOL)(μ-OAc)$_2$]$^+$ [7, 12].

The electronic absorption spectrum of **1** in MeCN solution consists of a broad band centered at 601 nm ($\epsilon = 7700$ l mol^{-1} cm^{-1}), which is characteristic of a phenolate-to-iron(III) charge transfer (CT) process [22]. An additional well resolved band with similar intensity is observed at 334 nm ($\epsilon = 7850$ l mol^{-1} cm^{-1}), which is also assigned to a phenolate-to-iron(III) CT transition. This interpretation is strongly corroborated by the similar spectral data of the [Fe$_2^{III}$(BBPPNOL)(μ-OAc)$_2$]$^+$ ion complex, for which detailed spectroelectrochemical studies have been described elsewhere [12].

A cyclic voltammogram of complex **1** in MeCN is displayed in Fig. 3. At scan rates of 50–200 mV s^{-1} two well defined quasi-reversible one-electron-transfer waves were detected at $E^1_{1/2}$ -0.57 V and $E^2_{1/2}$ of -1.15 V versus Fc$^+$/Fc. These waves correspond to Fe$_2^{III}$/Fe^{II}Fe^{III} and Fe^{II}Fe^{III}/Fe$_2^{II}$ couples, respectively, which are reported [12] to occur at -0.61 and -1.0 versus Fc$^+$/Fc for the [Fe$_2^{III}$(BBPPNOL)(μ-OAc)$_2$]$^+$ complex. However, due to the presence of terminal phenolate groups, these couples lie at more negative potentials than those observed in the BIMP$^-$ and BPMP$^-$ complexes in which the Fe atoms are bonded to imidazolyl or pyridyl terminal groups [13, 15].

From this information, we must conclude that additional appropriate modifications on the H$_3$BBPMP and H$_3$BBPPNOL ligands are necessary to obtain more adequate models for PAPs. The synthesis of unsym-

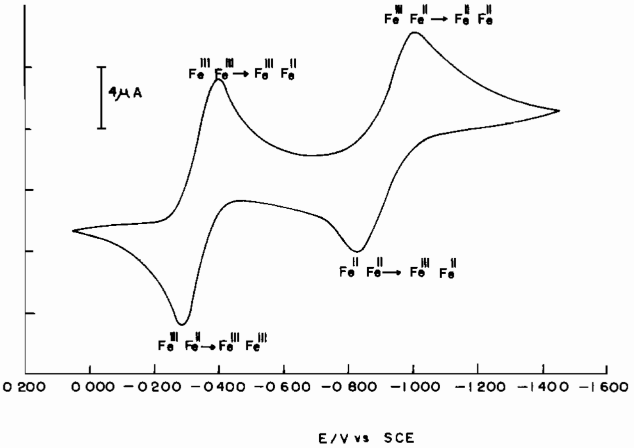

Fig 3. Cyclic voltammogram of **1** in MeCN (0.1 M $[Bu_4N][PF_6]$) supporting electrolyte, platinum working electrode, ferrocene internal standard, scan rate 100 mV s^{-1} (SCE = standard calomel electrode).

metrical analogues of H_3BBPMP containing only one phenolate-pendant arm and their binuclear iron complexes are in progress in our laboratory and will be the subject of future reports.

Supplementary material

The following tables are available from the authors on request: data collection and structure refinement parameters of the $Fe_2^{III}(BBPMP)(OAc)_2]ClO_4 \cdot H_2O$ complex; atomic parameters; bond distances; bond angles; anisotropic temperature factors; hydrogen atoms and list of observed and calculated structure factors (34 pages).

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