J. Braz. Chem. Soc., Vol. 9, No. 5, 426-429, 1998.
Printed in Brazil.

Note

A New Biomimetic Model for the Active Site of Oxovanadium(IV)-Transferrins – $[OV^{IV}(tf)]$

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Received: May 15, 1998

Reportamos neste trabalho, a síntese, a estrutura cristalina e propriedades espectroscópicas do novo complexo $[OV^{IV}(HBIMETEN)]$, $[H_3BIMETEN$ = *N*,*N*'-(2-hidroxibenzil)-*N*-(1-metilimidazol-2-il-metil)-*N*'-hidroxietil-etilenodiamina] como um exemplo de complexo $V^{IV}O^{2+}$ o qual contém grupos 1-metilimidazol e fenolato coordenados simultaneamente ao centro metálico. Este composto apresenta propriedades espectrais (EPR e UV-Vis) similares àquelas observadas na $[OV^{IV}(tf)]$.

The synthesis, X-ray crystal structure, and spectroscopic properties of the new coordination compound $[OV^{IV}(HBIMETEN)]$, $[H_3BIMETEN$ = *N* , *N*' - (2-hydroxybenzil) –*N*-(1-methylimidazole–2–yl-methyl)-*N*'-hydroxyethil-ethylenediamine] are reported as $V^{IV}O^{2+}$ complex example containing phenolate and 1-methylimidazole coordinated simultaneously to the metal center. The EPR and UV-Vis properties of the title compound are similar to those observed in $[OV^{IV}(tf)]$.

Keywords: *VO^{2+} complex, crystal structure, EPR, vanadium transferrin*

Introduction

Vanadium has an important role in many biological processes. Particularly it has been proposed that delivery of vanadium in higher organisms is performed by transferrin[1]. Transferrins are glycoproteins whose primary function is to bind and transport iron, but they also coordinate a wide variety of other metals including vanadium. They are a single polypeptide chain with two homologous lobes, denominated C- and N-terminal, each of which binds one metal ion[2a]. Despite the binding of iron(III)-transferrin has been established through crystallographic studies (NO_3 coordination and CO_3^{2-} as synergistic anion)[3], the coordination environment around the vanadium centre in vanadium-transferrins is not yet entirely known. It is well known that in the +3, +4, and +5 oxidation states, vanadium binds tightly to transferrin[4,5]. In an attempt to gain insight into the biological roles of vanadium, many recent studies have focussed on the coordination chemistry of this metal, in the oxidation states +3, +4 and +5, with biologically relevant ligands[6,7]. In the +4 oxidation state, a vanadyl complex structure with octahedral geometry having an NO_3 equatorial coordination (one tyrosinate, one aspartate, one histidine and one monodentate carbonate) has been proposed recently for vanadium human lactoferrin[5]. The coordination of histidine *trans* to the V=O bond has also been proposed[6]. This work is a continuation of a wide research program for the preparation and characterization of vanadium complexes of bioinorganic interest[7].

Experimental

Abbreviations

H_3BIMETEN, *N*,*N*'-bis-(2-hydroxybenzyl)-*N*-(2-methylimidazole)-*N*'-(2-hydroxyethyl)ethylenediamine; H_2BBIMEN, *N*,*N*'-bis-(2-hydroxybenzyl)-*N*, *N*'-(2-methylimidazole)ethylenediamine); H_2BBPEN, *N,N'*-bis(hydroxybenzyl)-*N,N'*-bis(pyridyl- methyl)ethylenediamine); HIMETEN, *N*-(2-methylimidazole)-*N'*-(2-hydroxyethyl) ethylenediamine; [OV^{IV}(tf)], vanadium(IV)-transferrin.

Synthesis

The ligand H_3BIMETEN was prepared in good yield (91.36%) by the condensation reaction of 1-methyl-2-imidazolecarboxyaldehyde[8] with *N*-(2-hydroxyethyl)ethylenediamine, followed by reduction with $NaBH_4$ and by alkylation of the diamine (HIMETEN) with 2-bromomethylphenyl acetate[9], by the route in Scheme 1. The complex [OV^{IV}(HBIMETEN)] (**1**) was prepared by refluxing a methanolic solution of $VOSO_4.H_2O$ (0.163 g, 1 mmol) and H_3BIMETEN (0.410 g, 1 mmol) with stirring for 1 h. To the reaction was added Et_3N (1 mL, 7.18 mmol), to yield a violet precipitate (0.32 g - 67.37%). Anal. Calc. for $C_{23}H_{30}N_4O_5V$: C, 55.98; H, 6.08; N, 11.35. Found: C, 55.63; H, 5.95; N, 10.96%. The precipitate was recrystallized in an acetonitrile-ethanol (1:1) solution at room temperature. After a few days crystals suitable for X-ray crystallography were filtered off, washed with 2-propanol and dried with ether.

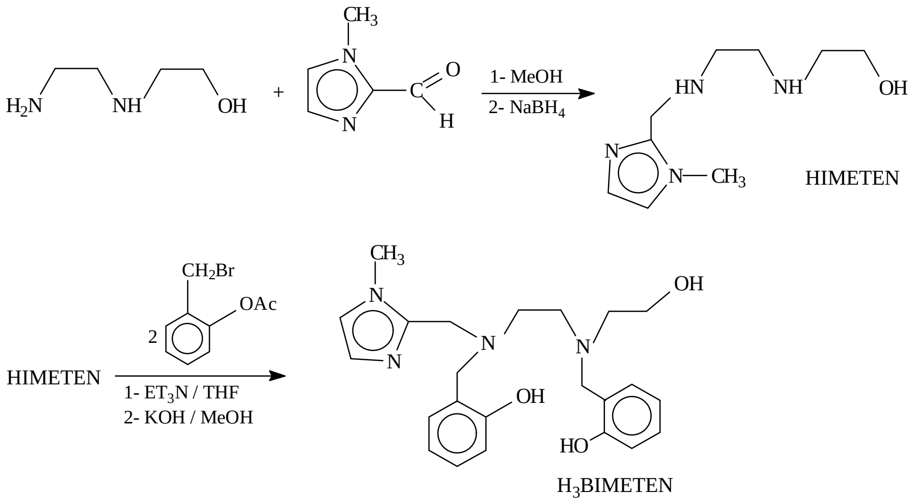
X-ray crystallography

Crystal data for $C_{23}H_{28}N_4O_4V$. 1/2 C_2H_5OH, M = 498.47, monoclinic, $P2_1/c$, (nº14), Z = 4, a = 15.304(3), b = 12.329(3), c = 12.441(3) Å, $\beta = 94.18(3)°$, V = 2341.2(9) $Å^3$, $D_c = 1.414$ g cm^{-3}, F(000) = 1048, $\mu = 0.465$ mm^{-1} for Mo-K_α radiation ($\lambda = 0.71073$ Å), crystal size 0.07 x 0.20 x 0.43 mm. Nonius CAD4 diffractometer, T = 293 K. Measured reflections: 4108, with 2971 unique reflections of which 1921 had $I > 2\sigma(I)$. The structure was solved by direct methods, full-matrix refinement on F^2, anisotropic refinement for all non-H atoms. One ethanol molecule was found to be disordered near an inversion center, with occupation factor of 1/2. The number of refined parameters was 307, R1 = 0.0846, wR2 = 0.2465. Crystallographic calculations were performed using the MOLEN, SHELXS97, SHELXL97 and ZORTEP computer program packages[10].

Results and Discussion

The structure and atomic numbering scheme of 1 are illustrated in Fig. 1. The vanadium (IV) ion lies in a distorted octahedral environment, in which two phenolate oxygen, one amine and one imidazole nitrogen atoms in *cis* positions form the equatorial plane. The other amine nitrogen atom of the ethylenediamine backbone, in the *trans*-position with respect to the terminal oxo group, and that oxo atom completes the coordination sphere of the vanadium center while the hydroxyl group remains uncoordinated. The VO distance is short [1.610(6) Å], indicating the double bond character typical of vanadyl (IV) complexes[7c,d,e,f]. This value is slightly longer compared to that [1.590(1) Å] in [OV^{IV}(HBBIMEN]$^+$ [7e]. As expected, the V-N$_{(amine)}$ bond distance of 2.372(6) Å *trans* to the V=O bond in 1, is 0.157 Å longer than the V-N$_{(amine)}$ bond in the equatorial plane and is a consequence of the strong *trans* influence of the oxo group. The V-O$_{(phenolate)}$ [1.949(6) and 1.931(6) Å] bond distances in 1 are longer than that detected in [OV^{IV}(HBBIMEN]$^+$ [1.905(8) Å] due to a higher electronic density on the vanadium center in 1 – N_3O_3 coordination compared to [OV^{IV}(HBBIMEN)]$^+$ - N_4O_2 coordination. The V-N$_{(imidazole)}$ [2.120(7) Å] bond distance in the equatorial plane of 1 is 0.040(8) Å longer than those found in [OV^{IV}(HBBIMEN)]$^+$ [av. 2.080(9) Å] and is a reflection of the weak *trans* influence caused by the phenolate bond in 1. The above results reveal that, at least to some extent, 1 is more distorted that [OV^{IV}(HBBIMEN)]$^+$.

The electronic spectra of **1** measured in DMF in the visible region reveals the following transitions at λ_{max}/nm (ε / dm^3 mol^{-1} cm^{-1}): 881 (20.08), 538 (76.28) and 441



Scheme 1. Synthesis of the ligand H_3BIMETEN.

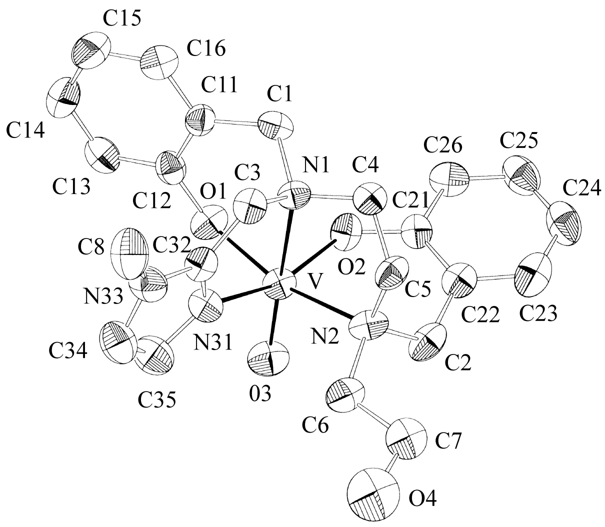


Figure 1. X-ray structure of 1, showing the atom-labeling scheme, at 50% probability level. Selected bond lenghts (Å) and angles (°): V-O3 1.610(6), V-O2 1.931(6), V-O1 1.949(6), V-N31 2.120(7), V-N2 2.215(7), V-N1 2.372(6), O3-V-O2 105.2(3), O3-V-O1 102.9(3), O2-V-O1 84.8(2), O3-V-N31 95.7(3), O2-V-N31 158.9(3), O1-V-N31 88.3(2), O3-V-N2 93.7(3), O2-V-N2 88.6(2), O1-V-N2 163.2(3), N31-V-N2 92.5(3), O3-V-N1 165.2(3), O2-V-N1 86.5(2), O1-V-N1 87.0(2), N31-V-N1 73.3(2), N2-V-N1 77.2(2) .

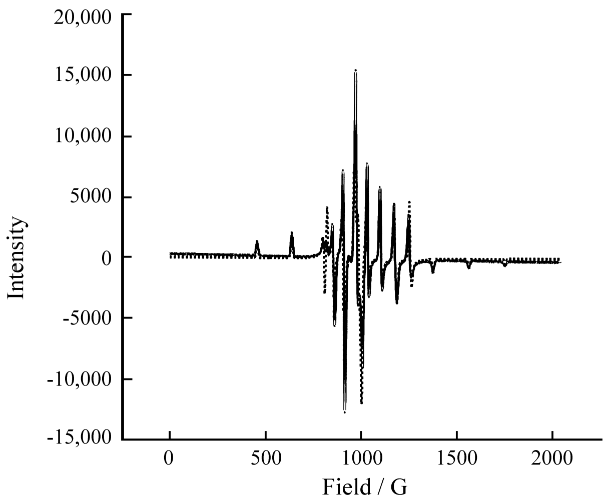


Figure 2. 2 X-band EPR spectrum of 1 in DMF at 77 K. (xxx) Experimental spectrum and (—) simulated spectrum using the Winepr SimFonia Program, the molecular peak-peak linewidths referred to the g tensor axes of $\Delta B_x = 9.00$, $\Delta B_y = 12.00$, $\Delta B_z = 8.00$ G and a Gaussian line-shape function. The Hamiltonian parameters are $g_x = 1.9799$, $g_y = 1.9789$, $g_z = 1.9436$, $A_x = 57.55$, $A_y = 57.05$, and $A_z = 164.50 \times 10^{-4}$ cm^{-1}.

(100.78). According to Ballhausen and Gray[11], the weak absorption at 881 nm is attributed to the d-d transition $d_{xy} \rightarrow d_{xz,yz}$ whereas those at 538 and 441 nm involve the $d_{x^2-y^2}$ and the d_{z^2} orbitals in compounds of C_{4v} symmetry, as in [OV^{IV}(HBBIMEN)]PF$_6$ for which the corresponding transitions are observed at λ_{max}/nm (ε/ dm^3 mol^{-1} cm^{-1}): 826 (46), 537 (76) and 380 (462)[12]. In agreement with the X-ray crystal data previously described, **1** is a little more distorted than [OV^{IV}(HBBIMEN)]PF$_6$ but not enough to split the $d_{xy} \rightarrow d_{xz,yz}$ transitions as in [OV^{IV}(tf)][4b] and [OV^{IV}(BBPEN)][7c].

The X-band EPR spectrum of a frozen solution of **1** in DMF together with the simulated spectrum is shown in Fig. 2. The Hamiltonian parameters obtained from the spectrum of **1**, demonstrate the low symmetry geometric structure of the molecule, as can be observed in other vanadyl complexes previously reported in the literature[2b]. The pseudoaxial (because the parameters g_x and g_y are very similar) distortion is in agreement with X-ray diffraction data and the electronic absorption spectrum. However, this little in-plane observable anisotropy, $|g_x - g_y| = 0.001$, $|a_x - a_y| = 0.5 \times 10^{-4}$ cm^{-1}, demonstrates that distortions in **1** are somewhat little more pronounced than those observed in [OV^{IV}(HBBIMEN)]$^+$, in which the in-plane anisotropy is not observable. The smaller values of the g parameters for an N_2O_2 equatorial coordination are consistent with the d → d transitions with lower energy found in **1**, compared to the values observed in [OV^{IV}(HBBIMEN)]PF$_6$ ($g_x = g_y = 1.9925$, $g_z = 1.9545$) which has an N_3O equatorial coordination, and consequently higher energy d → d transitions. The corresponding parameters found in the ovotransferrin[2c], a member of the family of the transferrins found in the white of eggs, are $g_z = 1.939$, $g_x = 1.978$, $g_y = 1.974$, $A_z = 163.9$, $A_x = 52.3$ and $A_y = 59.2 \times 10^{-4}$ cm^{-1}.

In summary, a V^{IV}O^{2+} complex containing a novel polyfunctional ligand has been prepared and characterized structurally and spectroscopically. In spite of the numerous VO^{2+} complexes with nitrogen and oxygen donor atoms described in the literature[6,7], neither of these species exhibit all the characteristic spectral (UV-VIS and EPR) and structural properties found in [V(tf)][2b,4b]. Recent studies on the transferrins[5], show that the form of the bound vanadium(IV) ion is VO^{2+} (vanadyl). These studies also proposed that each vanadyl ion is coordinated to two tyrosine residues, one histidine residue, a monodentate carbonate ion and to an aspartic acid. The EPR and UV-Vis spectral properties of the coordination compound [O=V^{IV}(HBIMETEN)] described here, are very similar to those found in the ovotransferrin[2c], therefore we can propose that **1** is a very interesting model for the [OV^{IV}(tf)] complex.

Acknowledgements

This work was supported by grants from PRONEX, CNPq, FINEP, and PADCT.

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