Models of Oxovanadium(iv) – Protein Interactions: The First Oxovanadium(iv) Complexes with Dipeptides**

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Vanadium is a trace element that produces significant physiological effects; for example, vanadate inhibits ion transport ATPases,11 phosphotyrosine phosphatases2 etc. Arguably, the most important physiological effect is the stimulation of glucose uptake and glucose metabolism, that is, the insulin-like properties of both vanadate3 and oxovanadium(iv) species.4 The efficacy and relative lack of toxicity of oxovanadium(iv) derivatives in animal models of diabetes makes them a potential oral therapy in human diabetes in general, and in those forms of the disease that are resistant to insulin in particular. The mode of action of oxovanadium(iv) species is still not understood. Cornman11 and co-workers have suggested that a possible mechanism of VO2+ action is the inhibition of protein tyrosine phosphatases (PTPases) by binding thiolate sulfur to VO2+. In addition, Saper6 and co-workers have recently reported an X-ray crystal structure of Yersinia PTPase with VO2+, where there is a covalent bond between vanadium and the sulfur of the 403-cysteine residue. The elucidation of the mode and the site of VO2+ action could provide valuable insight into the mechanism of insulin action as well as in the design of more potent oral insulin substitutes.

In order to understand the function of VO2+ species in diabetes and in various biological processes in general, it is first necessary to develop its coordination chemistry17 with biologically relevant ligands such as peptides and in particular sulphydryl-containing peptides in light of Cornman’s11 observation and Saper’s crystallographic characterization of VO2+ with Yersinia PTPase mentioned above. To date, several complexes of oxovanadium(iv)9–10 have been prepared and structurally characterized, but only with aromatic amidines. Herein we report the synthesis and structural and physicochemical characterization of the first oxovanadium(iv)–dipeptide complex with the sulphydryl-containing dipeptide N-(2-mercaptopropionyl)glycine (H2mpg), as well as the first synthesis of VO2+ with the dipeptides glycyglycine (ggly) and glycylalanyline (glyala).

Sequential addition of one equivalent of 1,10-phenanthroline (phen) and of an acetonirole solution containing one equivalent of H2mpg and five equivalents of triethylamine to a solution of VOCl2(C6H5CN)3 in acetonitrile yields the complex I. The reaction was carried out at a -15 °C. At this point two features are worth noting: 1) the ease with which VIVO2+ promotes amide E1,NH[VO2mpg][phen] 1

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hydrogen ionization, in marked contrast to almost all other cases with aromatic amides [8-10] where the ionization of hydrogen in the presence of $\text{V}^{4+}\text{O}^2$ takes place under reflux with the use of strong bases, and 2) the deprotonation of amide nitrogen at room temperature as revealed by solution studies (water) of vanadium(v) with dipeptides [11, 12]. Figure 1 shows a perspective view [13] of the anion of I. The vanadium atom in the anion of I has a severely distorted octahedral geometry. It is bonded to a tridentate mpg$^{3-}$ ligand at the sulfur atom, the deprotonated Namide atom N1, and one of the Ocarboxylato oxygens. Strong support for this comes from 14N Electron Spin Echo Envelope Modulation (ESEEM) experiments, which indicate that the dipeptide glycylglycine is bonded to $\text{V}^{4+}\text{O}^2$ center through the amide nitrogen, the deprotonated amide nitrogen, and one of the carboxylato oxygens.

The redox properties of I in acetonitrile have been studied by cyclic voltammetric and polargraphic techniques. The complex displays a reversible one-electron redox process [Eq. (a); $E_{1/2}$ $\text{V}^{4+}\text{O}(\text{mpg})(\text{phen})]$ $+ e^{-} \rightarrow [\text{V}^{4+}\text{O}(\text{mpg})(\text{phen})]$ $- E_{1/2} = -1.42$ V (versus normal hydrogen electrode). The electronic absorption spectrum of I in acetonitrile ($[\text{nm}]$, $[\text{cm}^{-1}]$) consists of five bands and a shoulder: 532 (970), 356 (22900), 225 (31500). The intense absorptions in the visible region of the spectrum are assigned as $S \rightarrow \text{V}^+$ charge transfer transitions. Continuous wave EPR spectra for the complexes 1, 2, and 3 were recorded at 40 K in $\text{C}_2\text{H}_5\text{OH}$. The calculated values [10] for $A_{\text{Namide}}$ ($35 \times 10^{-4}$, $36 \times 10^{-4}$, and $36 \times 10^{-4} \text{ cm}^{-1}$ for the complexes 1, 2, and 3, respectively) are slightly higher than the average $A_{\text{Namide}}$ value $[34 \times 10^{-4} \text{ cm}^{-1}]$ reported by Corma [11] and co-workers for oxovanadium(iv) center with various aromatic amides.

**Experimental Procedure**

All syntheses were carried out under an inert atmosphere (argon) and with dry and deoxygenated solvents distilled just prior to use.

Table 1. EPR parameters [a] for the complexes 1-3.

<table>
<thead>
<tr>
<th>Complex</th>
<th>$g_{xx}$</th>
<th>$g_{yy}$</th>
<th>$g_{zz}$</th>
<th>$A_{xx}$</th>
<th>$A_{yy}$</th>
<th>$A_{zz}$</th>
<th>$A_{XX}$, cm$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.956</td>
<td>1.987</td>
<td></td>
<td>52.1</td>
<td>151.1</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.951</td>
<td>1.984</td>
<td></td>
<td>54.8</td>
<td>158.9</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.951</td>
<td>1.984</td>
<td></td>
<td>54.8</td>
<td>159.0</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

[a] Errors: $g$ values $\pm 0.003$, hyperfine coupling constants $\pm 0.7 \times 10^{-4} \text{ cm}^{-1}$.

**Key Words:** EPR spectroscopy · peptides · solid-state structures · vanadium compounds

COMMUNICATIONS


[17] Crystal data for 1: CH3OH: C21H29N2O2SV [EtNH][Otmdg(phen)]-CH2OH: M = 541.56; monoclinic, space group P21/c; a = 14.828(2), b = 11.513(1), c = 16.637(2) Å, β = 112.736(4); V = 2196.3(5) Å3, Z = 4, μmax = 1.373 g cm−3, μ = 4.25 mm−1; max. absorption correction factor 1.60; 2θmax = 155.24; CuKα radiation, R = 0.028 ± 2% scan; reflections collected/unique: 3767/3579 (Rw = 0.0219/0.3577; parameters refined, 352; R1 = 0.069 (I > 2σI); 2794 reflections with I > 2σI, 0.0576/0.1579; GOF = 1.029; [d/σ(d)]max < 0.003; [σ(p)/σ(θ) = 0.373] − 0.308 e Å−3, structure solution and refinement with the programs SHELXS-86 and SHELXL-93; H atoms of 1,3,5-phenanthroline were located by difference maps and refined isotropically, the rest were introduced at calculated positions as riding on bonded atoms; all non-H atoms refined anisotropically (except atoms of the solvent methanol which refined isotropically with occupancy fixed at 10.3). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-179-98. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: int. code +441223 336-033, e-mail: deposit@ccdc.cam.ac.uk).


[24] The calculated Ai,eq values were derived from the relation Ai,eq = 2πN/Ai, where i denotes the different types of equatorial ligand donor positions (i = 1–4), n is the number of equatorial ligands of type i and Ai,i,i is the measured coupling constant (from model studies) when all four equatorial ligand donor groups are of type i. See N. D. Chasten in Biological Magnetic Resonance, Vol. 7 (Eds.: L. J. Berliner, J. Reuben), Plenum, New York, 1981, p. 53.

**Spontaneous Magnetization in a Sulfur–Nitrogen Radical at 36 K**


There has been considerable interest in the magnetic behavior of organic free radicals [1–2] and particularly in the development of materials that exhibit spontaneous magnetic order or ferromagnetism. The number of radicals of this type are few and have been based exclusively on NO radicals [3–5], with magnetic ordering temperatures of a few Kelvin. We now report a new phase of the sulfur–nitrogen dithiadiazolyl radical p-NC-C6F5-CNNSN2+ (1), which exhibits weak ferromagnetism at the unprecedentedly high temperature of 36 K. It is the first main-group radical to exhibit spontaneous magnetization above liquid helium temperature.

Radical 1 is a member of a large class of dithiadiazolyl radicals [6], which are particularly suitable for study as potential "organic metals". [7] Most dithiadiazolyl radicals are diamagnetic, associating to form dimers in the solid state [8] through an out-of-plane, spin-paired interaction between sulfur atoms. This dimerization energy is small and has been estimated at about 35 kJ mol−1 [9]. In order to prepare dithiadiazolyl radicals with unusual magnetic properties we must first overcome this dimerization process. This has been achieved in 1 by carefully chosen substituents, in which 1) in-plane cyano–sulfur interactions compete with the out-of-plane dimerization process and 2) fluoro–fluorine repulsions between molecules assist the break-up of the dimeric structure. The synthesis of 1 has been described previously [10]. It can be prepared as either of two polymorphs, the formation of which is dependent upon sublimation conditions. We recently reported [11] the structure and magnetic properties of the p-phase (1α) obtained by very rapid sublimation (120°C, 10−2 Torr) of crude 1. Phase 1α is paramagnetic at room temperature, and has an effective magnetic moment of 1.60 μB, slightly less than that expected for unpaired S 3/2 spins. It exhibits Curie–Weiss behavior (θ = -25 K) down to low temperature, at which point long-range magnetic order sets in with a Neel temperature of 8 K. [9] The X-ray crystal structure of this phase consists of chains of monomeric radical units packed in a head-to-tail manner. [9]

The β-phase of 1 (1β) forms as long, plasticly deformable needles by slow sublimation of 1 (100°C, 10−2 Torr). The structure [10] consists of discrete monomeric dithiadiazolyl radicals. In 1β the twist-angle between heterocyclic and aryl rings is more prominent than in 1α: the twist angles about the C–C bond are 88° and 128° in 1α and 1β, respectively. The structures

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