Model investigations for vanadium–protein interactions: first vanadium(III) complexes with dipeptides and their oxovanadium(IV) analogues

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Reaction of the dipeptides H₂Gly-Tyr and H₂Gly-Phe with VCl₃ and 1,10-phenanthroline affords the compounds [V(Gly-Tyr)(phen)]Cl·3MeOH 1 and [V(Gly-Phe)(phen)]Cl·3MeOH 2; aerial oxidation of the complexes 1 and 2 gives their oxovanadium(IV) analogues [VO(Gly-Tyr)(phen)] 3 and [VO(Gly-Phe)(phen)] 4, respectively; the X-ray crystal structure of 3 is reported.

Vanadium is an essential nutrient for higher animals,1 although this has not yet been clearly established as such to human life.2 Nevertheless, vanadium in vivo generates significant physiological responses;3 for example, vanadate inhibits ion transport ATP-ases,4 phosphotyrosine phosphatase,5 etc. Beyond dispute, the most important physiological response of vanadium is its insulin-mimetic properties.6 Our understanding of the mechanism of vanadium insulinnimetic action is still in its infancy.6 In addition to the above mentioned roles of vanadium, the oxovanadium(IV) center is an excellent EPR spectroscopic probe for various naturally occurring vanadoproteins and oxovanadium(IV)-substituted protein systems.7 Detailed structural, physicochemical and kinetic investigations on synthetic model complexes of vanadium with peptides, that are the most closely related models to proteins, will contribute greatly to our understanding of the mechanism of insulin mimetic action of vanadium as well as of its biological role in general. To date, there are only two vanadium(IV) complexes structurally characterized with the dipeptide glycylglycine and glycylalanine has also been reported.8 Herein, we describe the synthesis of the first vanadium(III) complexes with dipeptides, namely, with glycyl-L-tyrosine (Gly-Tyr) and glycyl-L-phenylalanine (Gly-Phe) and their oxovanadium(IV) analogues. The X-ray crystal structure of VO²⁺ with Gly-Tyr is reported, as well as the electrochemistry and the EPR spectra of the VO²⁺ compounds. To our knowledge, the structure of VO²⁺ with the dipeptide Gly-Tyr is the first example of a structurally characterized vanadium(IV) complex with a peptide.

Vanadium(III) chloride (2 mmol) was dissolved in methanol at ambient temperature, then the solution was cooled to −20 °C. Sequential addition of 1,10-phenanthroline (2 mmol), of the dipeptide (2 mmol) and an excess of triethylamine (10 mmol) to the vanadium solution, followed by slow warming under magnetic stirring to room temperature, induced a sequence of color changes (from red through red-brown to brown-purple) and resulted in the formation of the complexes [V(Gly-Tyr)(phen)]Cl·3MeOH 1 (yield 70%) and [V(Gly-Phe)(phen)]Cl·3MeOH 2 (yield 50%). Air oxidation of 1 and 2 gives their oxovanadium(IV) analogues, [VO(Gly-Tyr)(phen)] 3 (yield 80%) and [VO(Gly-Phe)(phen)] 4 (yield 65%), respectively. The elemental analyses for complexes 1–4 are in accord with the formulas given above.

The molecular structure of the complex 3 (Fig. 1), shows the vanadium atom possessing a severely distorted octahedral coordination. The vanadium atom is 3 ligated to a trigonate Gly-Tyr²⁻ ligand at the Namide atom N(11) the deprotonated Npeptide atom N(12) and one of the Ocarboxylate atoms O(14), as well as an oxo group O(1) and two phenanthenetin nitrogen N(1) and N(10) is 0.33 Å, above the mean equatorial plane, defined by the three ligating atoms of the dipeptide [N(11), N(12), O(14)] and a phenanthenitro nitrogen N(1), in the direction of the oxo ligand. The peptide functionality N(12)–C(12)O(12)C(11) [maximum deviation of C(12) is 0.02 Å] is planar within the limits of precision. The ligand Gly-Tyr²⁻ forms two five-membered fused chelate rings and is meridionally ligated to VO²⁺ center with the amine nitrogen and carbamylato oxygen atoms lying in trans position. The V–N peptide bond length [1.927(7) Å] is indicative of a very strong bond of the deprotonated peptide nitrogen to vanadium, and may reflect some V=O character due to donation of electron density from the deprotonated peptide nitrogen into metal d orbitals. The oxovanadium(IV)–amide N distance in complex 3 is significantly shorter (ca. 0.07 Å) than seen in the related complex [NHEt₃][VIVO(mpg)(phen)]Cl₃OH²⁻.5 5 [V–Namide = 1.997(4) Å] which is the only other oxovanadam(IV) complex which contains an aliphatic V–Namide bond. This significant difference could be ascribed to ligand constraints in 3 and to the weaker dianionic ligand set (Gly-Tyr²⁻) in complex 3, compared to trianionic ligand set (mpg²⁻) in complex 5, which results in a higher effective charge on the vanadium center and shorter V–N distances. Nevertheless, the V–Namide and V–Npeptide bond lengths in 3 are longer (ca. 0.03 and 0.06 Å, respectively) from the analogous distances found in the complexes [Cu(Gly-Tyr)(H₂O)₂]·2H₂O 6¹ [Pd(Gly-Tyr)-(cyd)]·6SH₂O 7¹² [complexes 6 and 7 are the only two other Gly-Tyr compounds with transition metal ions] but the V–Ocarboxylate bond distance in 3 is shorter (ca. 0.03 and 0.07 Å for 6 and 7 respectively); this is expected¹³ as the V=O²⁺ center

Fig. 1 The X-ray structure of 3. Selected interatomic distances (Å) and angles (°): V–O(1) 1.574(5), V–O(14) 1.946(5), V–N(1) 2.105(7), V–N(12) 1.927(7), V–N(11) 2.075(7), V–N(10) 2.351(7); N(1)–V–N(12) 106.9(3), N(1)–V–N(11) 91.5(3), N(1)–V–N(10) 89.3(3), O(14)–V–N(11) 95.1(2), O(4)–V–N(10) 90.2(2), O(1)–V–N(9) 92.7(2), N(1)–V–N(10) 92.7(2), O(1)–V–O(14) 103.5(3), O(1)–V–N(11) 98.0(3), O(14)–V–N(11) 154.3(3), N(12)–V–N(1) 161.1(3), N(11)–V–N(1) 103.3(3), N(12)–V–N(10) 90.0(2), N(11)–V–N(10) 81.3(2).
Table 1 EPR parameters for the complexes 3 and 4

<table>
<thead>
<tr>
<th>Compound</th>
<th>Donor set</th>
<th>$g_z$</th>
<th>$g_y$</th>
<th>$g_x$</th>
<th>$A_0$</th>
<th>$A_1$</th>
<th>$A_2$</th>
<th>$A_{\text{amide}}$</th>
</tr>
</thead>
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<tr>
<td>3</td>
<td>N$_2$O</td>
<td>1.982</td>
<td>1.984</td>
<td>1.952</td>
<td>53.0</td>
<td>58.0</td>
<td>160.0</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>N$_2$O</td>
<td>1.981</td>
<td>1.983</td>
<td>1.951</td>
<td>54.0</td>
<td>58.0</td>
<td>159.0</td>
<td>34</td>
</tr>
</tbody>
</table>

is considered a ‘hard acid’, Cu$^{2+}$ a borderline acid and Pd$^{2+}$ a soft acid and oxygen a harder base than nitrogen. The side chain aromatic ring is tilted to the equatorial coordination plane of vanadium (the dihedral angle between these planes is 31°) and in the opposite direction from it, in marked contrast to oxovanadium($IV$) complexes in methanol, which is characteristic of 1 : 1 axial ligand (O–$2$ in the coordination plane of the metal atom; this conformation of the aromatic ring is tilted to the equatorial coordination plane of the metal atom; this conformation of the aromatic ring is tilted to the equatorial coordination plane of vanadium ($O^2$–), that pushes away the aromatic ring.

The V–Cl stretch is absent from the IR spectra of complexes 1 and 2. This, in combination with the molar conductance of these complexes in methanol, which is characteristic of 1 : 1 electrolytes led us to the conclusion that the chloride atom is not coordinated to vanadium. The magnetic moments of complexes 1, 2 and 3 and 4 are in accord with the spin-only value expected for d$^2$ and d$^5$ systems, respectively.

The redox properties of 4 in acetonitrile (complexes 1, 2 and 3 are not soluble enough to be studied in MeCN) have been studied by cyclic voltammetric and polarographic techniques. The complex displays a reversible one-electron redox process [eqn. (1); $E_1/2 = –1.26$ V] which is almost identical to the amide value (34 cm$^{-1}$).

$[\text{V}^{IV}\text{O(Gly-Phe)(phen)}]e^– \rightarrow [\text{V}^{IV}\text{O}(\text{Gly-Phe})(\text{phen})] \quad E_{1/2} = –1.26$ V (1)

The continuous wave (cw) EPR parameters for the two oxovanadium($IV$) complexes 3 and 4 (Table 1) were determined by computer simulation of the experimental cw EPR spectrum. Comparison of the cw EPR data of the complexes 3 and 4 with those reported for various oxovanadium($IV$) species$^{14}$ with different equatorial donor sets (e.g., O$_2$, N$_2$O$_2$, N$_2$S$_2$, etc.) indicates that their equatorial donor set should be N$_2$O. Application of the additivity relationship$^{15}$ for complexes 3 and 4 gives an $A_0$ value of 159.6 $\times$ 10$^{-4}$ cm$^{-1}$ ($\approx 40.1 + 42.7 + 35 + 41.8$ $\times$ 10$^{-4}$ cm$^{-1}$) which is almost identical to the experimental values for both complexes (Table 1). Electron spin echo envelope modulation (ESEEM) experiments, that were performed on complexes 3 and 4 verified the existence of three different 14N atoms ligated to the equatorial plane of the oxovanadium($IV$) center. Thus, it was concluded that in solution, as well as in the solid state, the VO$^{2+}$ center is coordinated to three nitrogen atoms in the equatorial plane. The experimental values for $A_{\text{amide}}$ (35 $\times$ 10$^{-4}$ and 34 $\times$ 10$^{-4}$ cm$^{-1}$ for complexes 3 and 4, respectively) do not deviate from the average $A_{\text{amide}}$ value (34 $\times$ 10$^{-4}$ cm$^{-1}$) reported by Corrman et al.$^{16}$ for oxovanadium($IV$) complexes with various aromatic aminides and from the $A_{\text{amide}}$ for the complexes [V$^{IV}$O(Gly-Phe)(phen)]$\cdot$2MeOH and [V$^{IV}$O(Gly-Ala)-(phen)]$\cdot$MeOH (36 $\times$ 10$^{-4}$ cm$^{-1}$). Solution studies (water) of the VO$^{2+}$ with a number of peptides$^{17}$ also gave a value of ca. 35 $\times$ 10$^{-4}$ cm$^{-1}$ for $A_{\text{amide}}$.

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Notes and References

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† Crystal data: 3, C$_2$H$_5$N$_2$O$_2$V, $M = 483.36$, orthorhombic, space group $P2_12_12_1$; $a = 6.9130(2)$, $b = 12.4343(5)$, $c = 23.7833(9)$ Å, $U = 2084.37(13)$ Å$^3$, $Z = 4$, $D_p = 1.57$ g cm$^{-3}$; crystal dimensions $0.04 \times 0.12 \times 0.27$ mm, $\mu = 0.53$ mm$^{-1}$; 8496 data collected, 3049 data unique, 2999 data used; $F(000) = 992$, 303 parameters, $R_1 = 0.0714$, $wR_2 = 0.1491$ with $l > 2\sigma (I)$. Data were collected using small slices on a Siemens SMART system. The absolute chirality was established by the Flack parameter, 0.03(6). CCDC 1827520.

10 Hmpg is the pseudopeptide N-(2-mercaptopropionyl)glycine.

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