# 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 $H_2$Gly-Tyr and $H_2$Gly-Phe with $VCl_3$ 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 insulinomimetic 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 insulinomimetic action of vanadium as well as of its biological role in general. To date, there are only two vanadium(V) complexes structurally characterized with the dipeptide glycylglycine.[8a,b] The preparation of two vanadium(IV) compounds with the dipeptides glycylglycine and glycylalanine has also been reported.[8c] 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 $VO^{2+}$ with Gly-Tyr is reported, as well as the electrochemistry and the EPR spectra of the $VO^{2+}$ compounds. To our knowledge, the structure of $VO^{2+}$ 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** is ligated to a tridentate Gly-Tyr$^{2-}$ ligand at the $N_{amine}$ atom N(11) the deprotonated $N_{peptide}$ atom N(12) and one of the $O_{carboxylato}$ atoms O(14), as well as an oxo group O(1) and two phenanthroline nitrogens N(1) and N(10) and 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 phenanthroline 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-Tyr$^{2-}$ forms two five-membered fused chelate rings and is meridionally ligated to $VO^{2+}$ center with the amine nitrogen and carboxylato 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=N character[9] due to donation of electron density from the deprotonated peptide nitrogen into metal d orbitals. The oxovanadium(IV)–amidate N distance in complex **3** is significantly shorter (*ca.* 0.07 Å) than seen in the related complex $[NHEt_3][V^{IV}O(mpg)(phen)]CH_3OH$[8c,10] **5** [$V–N_{amide}$ = 1.997(4) Å] which is the only other oxovanadium(IV) complex which contains an aliphatic $V–N_{amide}$ bond. This significant difference could be ascribed to ligand constraints in **3** and to the weaker dianionic ligand set (Gly-Tyr$^{2-}$) in complex **3**, compared to trianionic ligand set (mpg$^{3-}$) in complex **5**, which results in a higher effective charge on the vanadium center and shorter V–N distances. Nevertheless, the $V–N_{amide}$ and $V–N_{amine}$ bond lengths in **3** are longer (*ca.* 0.03 and 0.06 Å, respectively) from the analogous distances found in the complexes $[Cu(Gly-Tyr)(H_2O)_2]·2H_2O$ **6**[11] [Pd(Gly-Tyr)-(cyd)]·$6.5H_2O$ **7**[12] [complexes **6** and **7** are the only two other Gly-Tyr compounds with transition metal ions] but the $V–O_{carboxylato}$ bond distance in **3** is shorter (*ca.* 0.03 and 0.07 Å for **6** and **7** respectively); this is expected[13] as the $V^{IV}O^{2+}$ center

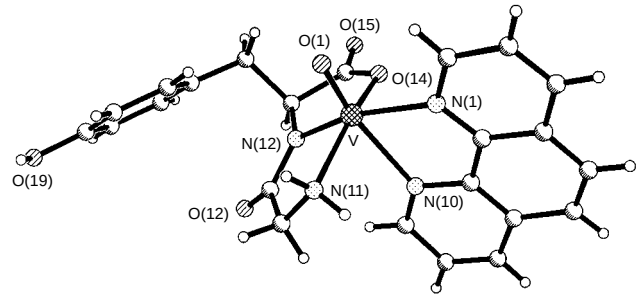


**Fig. 1** The X-ray structure of **3**. Selected interatomic distances (Å) and angles (°): V–O(1) 1.574(5), V–O(14) 1.946(5), V–N(1) 2.105(7), V–N(12) 1.927(7), V–N(11) 2.075(7), V–N(10) 2.351(7); O(1)–V–N(12) 106.9(3), N(12)–V–O(14) 80.2(2), N(12)–V–N(11) 78.8(3), O(1)–V–N(1) 91.5(3), O(14)–V–N(1) 91.6(2), O(1)–V–N(10) 162.7(3), O(14)–V–N(10) 82.7(2), N(1)–V–N(10) 72.0(2), O(1)–V–O(14) 103.5(3), O(1)–V–N(1) 98.0(3), O(14)–V–N(11) 153.4(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**

| Compound | Donor set | $g_x$ | $g_y$ | $g_z$ | $10^{-4}$ $A$/cm$^{-1}$ $A_x$ | $A_y$ | $A_z$ | $A_{z,amide}$ |
|---|---|---|---|---|---|---|---|---|
| **3** | $N_3O$ | 1.982 | 1.984 | 1.952 | 53.0 | 58.0 | 160.0 | 35 |
| **4** | $N_3O$ | 1.981 | 1.983 | 1.951 | 54.0 | 58.0 | 159.0 | 34 |

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 complexes **6** and **7** where the aromatic ring is roughly above the coordination plane of the metal atom; this conformation of the tyrosine residue in **3** may be imposed by the presence of the axial ligand ($O^{2-}$), 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**, **4** are in accord with the spin-only value expected for $d^2$ and $d^1$ 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 voltametric and polarographic techniques. The complex displays a reversible one-electron redox process [eqn. (1); $E_{\frac{1}{2}}$ *vs.* NHE].

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

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.*, $O_4$, $N_2O_2$, $N_2S_2$, *etc.*) indicates that their equatorial donor set should be $N_3O$. Application of the additivity relationship[15] for complexes **3** and **4** gives an $A_z$ value of $159.6 \times 10^{-4}$ cm$^{-1}$ [ = $(40.1 + 42.7 + 35 + 41.8) \times 10^{-4}$ 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 $^{14}N$ 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 $A_{z,amide}$ ($35 \times 10^{-4}$ and $34 \times 10^{-4}$ cm$^{-1}$ for complexes **3** and **4**, respectively) do not deviate from the average $A_{z,amide}$ value ($34 \times 10^{-4}$ cm$^{-1}$) reported by Cornman *et al.*[16] for oxovanadium(IV) complexes with various aromatic amides and from the $A_{z,amide}$ for the complexes $[V^{IV}O(Gly\text{-}Gly)(phen)]\cdot 2MeOH$ and $[V^{IV}O(Gly\text{-}Ala)(phen)]\cdot MeOH$ ($36 \times 10^{-4}$ 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 $A_{z,amide}$.

We gratefully acknowledge support of this research by the Greek General Secretariat of Research and Technology (Grant no. 1807/95) and Mrs F. Masala for typing the manuscript.

## Notes and References

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† *Crystal data*: **3**, $C_{23}H_{20}N_4O_5V$, $M$ = 483.36, orthorhombic, space group $P2_12_12_1$, $a$ = 6.9130(2), $b$ = 12.4343(5), $c$ = 23.7833(9) Å, $U$ = 2044.37(13) Å$^3$, $Z$ = 4, $D_c$ = 1.57 g cm$^{-3}$; crystal dimensions 0.04 × 0.12 × 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 $I > 2\sigma(I)$. Data were collected using small slices on a Siemens SMART system. The absolute chirality was established by the Flack parameter, 0.03(6). CCDC 182/750.

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*Received in Basel, Switzerland, 3rd November 1997; 7/07910I*