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$V^{IV}O$ Complexes of Bis(imidazol-2-yl) Derivatives: A Potentiometric, Spectroscopic and DFT Study

Katalin Várnagy,[a] Timea Csorba,[a] Dóra Kiss,[a] Eugenio Garribba,*[b] Giovanni Micera,*[b] and Daniele Sanna[c]

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The complexation of the $V^{IV}O$ ion with four amino acid derivatives of bis(imidazol-2-yl)methylamine [*N*-glycyl-bis(imidazol-2-yl)methylamine = Gly-BIMA, *N*-α-aspartyl-bis(imidazol-2-yl)methylamine = α-Asp-BIMA, *N*-α-glutamyl-bis(imidazol-2-yl)methylamine = α-Glu-BIMA and *N*-histidyl-bis(imidazol-2-yl)methylamine = His-BIMA] was studied in aqueous solution through the combined application of potentiometric and spectroscopic (UV/Vis and EPR) techniques. For comparison, the complexing capability of three simple bis(imidazol-2-yl) derivatives [bis(imidazol-2-yl)methane = BIM, bis(imidazol-2-yl)methylamine = BIMA and bis(imidazol-2-yl)-nitromethane = BINM] and two benzyloxycarbonyl (Z) derivatives (Z-Gly-BIMA and Z-Ala-BIMA) was reported. Mono- and bis-chelated species with the (N_{im}, N_{im}) donor set were formed in both acid and neutral pH conditions, with the bis-chelated complexes being characterised by a *cis-trans* isomerism. In the basic pH range the complexation process continues with the formation of a mono-hydroxo *cis*-VOL_2H_{-1} complex in systems with BIM, BIMA and BINM, and with the deprotonation and coordination of the amide nitrogen to give $VOLH_{-1}$ and $VOLH_{-2}$ in those with Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA and His-BIMA. The results demonstrate that the bis(imidazol-2-yl)methyl residue is an anchoring group of intermediate strength, capable of avoiding extensive hydrolysis of the $V^{IV}O$ ion in the presence of a slight excess of ligand (L/M from 3:1 to 5:1). DFT calculations with progressively more complex basis sets were performed in order to obtain information on the structure of the $VOLH_{-1}$ and $VOLH_{-2}$ complexes. Finally, a discussion on the ^{51}V anisotropic parallel hyperfine coupling constant ($A_{\parallel}$) of $VOLH_{-1}$ and $VOLH_{-2}$ and on the EPR properties connected to the V–N^-(amide) bond in $V^{IV}O$ complexes is presented.

Introduction

Vanadium plays a number of roles in biological systems.[1] It is accumulated by tunicates (ascidians or sea squirts)[2] and the fan worm *Pseudopotamilla occelata*,[3] and by some species of the mushroom genus *Amanita*.[4] Vanadium is also present in two enzymes, vanadium-dependent haloperoxidases,[5] and nitrogenase.[6] In the human organism it elicits a number of physiological responses, for example, the inhibition of phosphate-metabolising enzymes,[7] such as phosphatases, ribonuclease and ATPases, and its compounds show insulin-mimetic activity.[8]

The presence of vanadium in all these systems suggests it interacts with biomolecules. Among the biomolecules present in intra- and extra-cellular fluids, proteins and peptides have a special importance because of their high amount in the cellular environment and their possible interaction with the metal ions through a number of donor groups. For instance, glutathione is believed to play an important role in the processes of reduction of V^V to $V^{IV}O$ and in the subsequent complexation reactions.[9]

The interaction of vanadium, mainly in the oxidation states +IV and +V, with different proteins and enzymes has been reported in the literature.[10] Of special importance is interaction with human transferrin (hTF) and human serum albumin (HSA), since they could be involved in the transport of vanadium and insulin-mimetic compounds towards physiological target sites.[11–16]

Oligopeptides are the most closely related models for proteins; they may mimic specific metal ion binding sites, for example, GlyGlyHis for serum albumin.[17] Detailed studies on synthetic models of the vanadium–protein interaction can greatly contribute to the knowledge of its biological activity. Oligopeptides can interact with a metal ion through the terminal amino and carboxylate groups, intermediate peptide bond and side-chain donors, but all these groups are not strong enough to keep metal ions in solution at the physiological pH. However, they can play the role of "anchoring group" and promote the deprotonation of the

[a] Department of Inorganic and Analytical Chemistry, University of Debrecen,
4010 Debrecen, Hungary
[b] Department of Chemistry, University of Sassari,
Via Vienna 2, 07100 Sassari, Italy
Fax: +39-079-212069
E-mail: garribba@uniss.it
[c] Istituto C.N.R. di Chimica Biomolecolare,
Trav. La Crucca 3, 07040 Li Punti, Sassari, Italy
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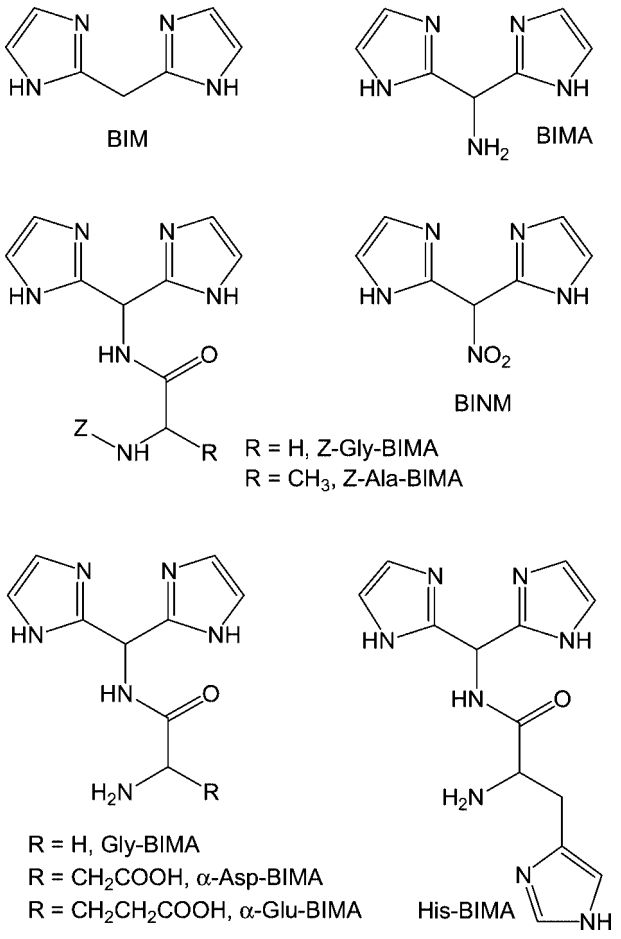
amide bond and its coordination in the $–N^-$ form, as proved with Pt^{II}, Pd^{II}, Cu^{II}, Ni^{II}, Zn^{II} and Co^{II}.[18]

Recently, the role of the anchoring groups was studied with $V^{IV}O$ and it was found that their effectiveness in promoting peptide amide deprotonation and coordination follows the order: phenolate-O^- > alcoholate-O^- > thiolate-S^- > carboxylate-COO^- > amino-NH_2.[19] Subsequent results demonstrated that a histidyl residue in the *N*-terminal position can act as a valid anchor because the coordination of the amino group is assisted by the imidazole nitrogen of the side-chain.[20] Many examples of $V^{IV}O$ complexes containing a V–N^-(amide) bond, both in solution and in the solid state, have been characterised in the last few years.[19–21]

A particularly interesting case of anchoring group is represented by the bis(imidazol-2-yl)methyl moiety, in which two imidazole rings are linked via a methylene group, since it can potentially mimic the binding sites and catalytic activities of the metal-enzymes with the binding of imidazole nitrogen donors belonging to histidine residues (for example, copper and zinc enzymes).[22] It has been proved that amino acid derivatives containing the bis(imidazol-2-yl)-methyl residue form very stable complexes with Cu^{II}, Zn^{II}, Ni^{II} and Co^{II} ions, promoting the deprotonation and coordination of the amide nitrogens.[23]

In this work, we report the complexation of the $V^{IV}O$ ion with four amino acid derivatives of bis(imidazol-2-yl)-methylamine: *N*-glycyl-bis(imidazol-2-yl)methylamine (Gly-BIMA), *N*-α-aspartyl-bis(imidazol-2-yl)methylamine (α-Asp-BIMA), *N*-α-glutamyl-bis(imidazol-2-yl)methylamine (α-Glu-BIMA) and *N*-histidyl-bis(imidazol-2-yl)methylamine (His-BIMA). In addition, two protected benzyloxycarbonyl (Z) derivatives were considered, where the terminal amino group of glycine and alanine was transformed into a Ph–CH_2–O–C(O)–NH– function: Z-Gly-BIMA and Z-Ala-BIMA. This allows us to evaluate how the transformation of an amino into a carbamate function, which can be considered as an analogue of the peptide group, modifies the complexation process. Bis(imidazol-2-yl)methane (BIM), bis(imidazol-2-yl)methylamine (BIMA) and bis(imidazol-2-yl)nitromethane (BINM) were studied for comparison. The structure of all the examined ligands is reported in Scheme 1. The study was performed through the combined application of potentiometric and spectroscopic (UV/Vis and EPR) techniques. DFT calculations were used to obtain information on the structure of $V^{IV}O$ complexes containing a V–N^-(amide) bond.



Scheme 1. Structure of the ligands (Z = benzyloxycarbonyl).

Results and Discussion

BIM, BIMA, BINM, Z-Gly-BIMA and Z-Ala-BIMA

All these ligands have two titrable protons in water and can be indicated in the fully protonated form as H_2L. The two protons belong to the two imidazole rings except for BIMA, for which the higher pK_a refers to the deprotonation of the ammonium group $–NH_3^+$. Protonation constants of the ligands are reported in Table 1. The measured pK_a values are comparable with those already reported for BIM and BIMA.[23a] As previously observed, the interaction between the two aromatic rings decreases the first pK_a value in the bis(imidazol-2-yl)methyl moiety with respect to imidazole.[23a] Substitution at the methylene group has a marked effect on the pK_a values of the ligands; the positive charge on the ammonium group results in a further decrease in the basicity of the aromatic nitrogens and the first pK_a of BIMA cannot be determined. In the case of BINM an increase of acidity of one imidazole group can be observed [pK_{a1} = logβ(H_2L) – logβ(HL) is 4.00 for BINM and 4.72 for BIM]; the formation of the hydrogen bond between the two aromatic nitrogens, however, results in a decrease of acidity of the second imidazole group.

If the amino group of BIMA is transformed into an amide nitrogen the decrease of pK_a values is smaller than for BIMA itself, but the imidazole nitrogens are still less basic than those of BIM. This is well reflected by the pK_a of the two imidazole nitrogens of the bis(imidazol-2-yl)methyl moiety of Z-Gly-BIMA and Z-Ala-BIMA (Table 1). Their values, however, are in good agreement with those of peptide derivatives of the bis(imidazol-2-yl)methyl group with a protected terminal amino group (e.g. Ac-ProLeuGly-BIMA).[23a]

All the five ligands show analogous complexing behaviour, different from that of the derivatives of amino acids (see below). Stability constants of the $V^{IV}O$ complexes are

Table 1. Stability constants (logβ) of proton and $V^{IV}O$ complexes for BIM, BIMA, BINM, Z-Gly-BIMA, Z-Ala-BIMA at 25.0 ± 0.1 °C and I = 0.2 M (KCl).[a]

Species	BIM	BIMA	BINM	Z-Gly-BIMA	Z-Ala-BIMA
H_2L	11.65(1)	10.52(1)	12.08(1)	9.19(2)	8.86(1)
HL	6.93(1)	6.46(1)	8.08(1)	5.82(1)	5.65(1)
pK_a(Im_1)	4.72	<1	4.00	3.37	3.21
pK_a(Im_2)	6.93	4.06	8.08	5.82	5.65
pK_a(NH_2)		6.46			
VOLH		10.01(1)			
VOL	7.26(1)	6.75(1)	9.21(2)	6.22(1)	6.15(1)
VOL_2H_2		19.56(5)			
VOL_2	12.94(2)	12.07(1)	16.62(3)	11.28(2)	10.95(2)
$(VO)_2L_2H_{-2}$	6.95(5)	6.08(4)	11.30(7)	5.27(6)	4.98(6)
VOL_2H_{-1}	5.80(5)	5.10(3)	8.86(6)		
pK(VOL_2)[b]	7.14	6.97	7.76		

[a] The uncertainties (σ values) of the protonation and stability constants are given in parentheses. [b] pK(VOL_2) = logβ(VOL_2) – logβ(VOL_2H_{-1}).

reported in Table 1. From these data, the distribution curves of the species as a function of pH can be obtained; as an example, the distribution diagram for the system with BIM with a ligand-to-metal molar ratio of 5:1 is represented in Figure 1.

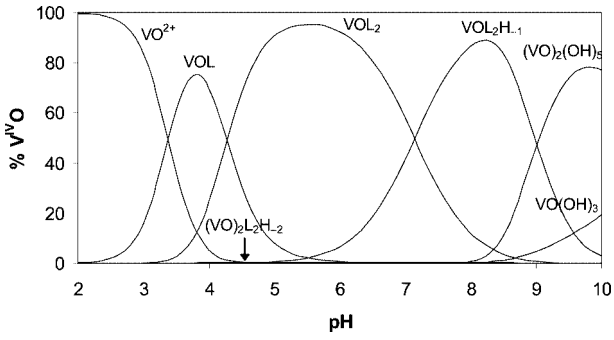


Figure 1. Species distribution for the $V^{IV}O$/BIM system as a function of pH with a ligand-to-metal molar ratio of 5:1 and a $V^{IV}O$ concentration of 1 mM.

In all the systems a mono-chelated VOL complex in acid solution, a bis-chelated VOL_2 in the pH range 4–7, and a mono-hydroxo VOL_2H_{-1} species above pH 7 are formed. With BIMA, besides VOL and VOL_2, VOLH and VOL_2H_2 exist, because of the presence of one and two additional protons on the amino group (Table 1). $(VO)_2L_2H_{-2}$ is probably an EPR-silent dimeric di-μ-hydroxo complex with antiferromagnetic coupling between the two $V^{IV}O$ ions.[24]

The complexation reactions can be followed by EPR spectroscopy, since the anisotropic hyperfine coupling constant along the z axis ($A_\parallel$) between the unpaired electron and the nucleus of ^{51}V in tetragonal complexes of the $V^{IV}O$ ion is particularly sensitive to the donors coordinated in the equatorial plane. $A_\parallel$ can be calculated from the sum of the contribution of each equatorial donor function, according to the "additivity rule" proposed by Wüthrich,[25] and subsequently developed by Chasteen, see Equation (1).[26]

$$A_\parallel = \sum_{i=1}^{4} A_\parallel(\text{donor i}) = A_\parallel(\text{donor 1}) + A_\parallel(\text{donor 2}) + A_\parallel(\text{donor 3}) + A_\parallel(\text{donor 4}) \quad (1)$$

This is an empirical rule that allows one to correlate $A_\parallel$ to the number and type of ligands present in the equatorial plane of the $V^{IV}O$ ion and has been proved and accepted in a large number of subsequent works.[27] The contribution to $A_\parallel$ is approximately inverse to the electron donor capacity of the ligand, with the most donating ligands contributing the least to the hyperfine coupling constant $A_\parallel$. Usually, the experimental $A_\parallel$ falls in the range of ca. 3×10^{-4} cm^{-1} with respect to the calculated value.[26,27]

EPR parameters for the complexes formed by BIM, BIMA, BINM and Z-Gly-BIMA are listed in Table 2. Anisotropic EPR spectra, recorded on frozen samples as a function of pH, for the system with BIM are displayed in Figure 2.

According to the potentiometric data (Figure 1), with a total $V^{IV}O$ concentration of 4 mM and a total BIM concentration of 20 mM, the first species is recognised between pH 3 and 4 as the mono-chelated complex VOL. Spectral parameters support a [(N_{im}, N_{im}); H_2O; H_2O] equatorial donor set (Scheme 2).[26]

At pH values higher than 4, the appearance of two new sets of resonances attributable to a complex with VOL_2 stoichiometry is detected (Figure 2). Since in the pH range 4.5–7.5 we observe the same EPR spectra with the presence of two species with an almost identical relative amount, it is obvious to suppose that these are the two isomeric *cis* and *trans* forms of the species VOL_2.

In bis-chelated $V^{IV}O$ complexes, *cis* species are hexacoordinate with one solvent molecule coordinated in the fourth equatorial position; *trans* species can be penta- or hexacoordinate according to the absence or presence of a solvent molecule weakly bound in the axial position, which can be revealed through the combined application of IR and UV/Vis spectroscopy.[28] As usual, because of the higher contri-

Table 2. EPR parameters of $V^{IV}O$ complexes.[a]

Ligand	VOL[b]		*cis*-VOL_2[c]		*trans*-VOL_2[d]		*cis*-VOL_2H_{-1}[e]		$VOLH_{-1}$[f]			$VOLH_{-2}$[g]		
	$g_\parallel$	$A_\parallel$	$g_\parallel$	$A_\parallel$	$g_\parallel$	$A_\parallel$	$g_\parallel$	$A_\parallel$	$g_\parallel$	$A_\parallel$ exp.	$A_\parallel$ calcd.	$g_\parallel$	$A_\parallel$ exp.	$A_\parallel$ calcd.
BIM	1.948	169.5	1.950	164.3	1.959	159.7	1.956	161.0						
BIMA	1.946	169.2	1.951	164.2	1.958	158.7	1.951	160.8						
BINM	1.950	167.6	1.951	163.0			1.952	159.1						
Z-Gly-BIMA	1.947	169.5	1.952	164.1	1.958	158.9								
Gly-BIMA	1.947	169.5	1.953	165.2	1.961	158.3			≈1.952–1.954[h]	≈163–165[h]	163.6	1.954	160.0	158.9
α-Asp-BIMA	1.947	168.7	1.950	164.8	1.958	158.2			≈1.952–1.954[h]	≈163–165[h]	163.6	1.953	158.5	158.9
α-Glu-BIMA	1.953	170.3	1.954	163.7	[i]	[i]			≈1.952–1.954[h]	≈163–165[h]	163.6	1.956	159.7	158.9
His-BIMA	1.949	169.8	1.951	164.9	1.958	158.4			≈1.952–1.954[h]	≈163–165[h]	163.6	1.952	160.0	158.9

[a] $A_\parallel$ measured in 10^{-4} cm^{-1}. [b] Species characterised by the [(N_{im}, N_{im}); H_2O; H_2O] donor set; in the systems with BIMA, Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA and His-BIMA, VOL can have various degrees of protonation (see Table 1 and Table 3). [c] Species characterised by the [(N_{im}, N_{im}); (N_{im}, N_{im}^{ax}); H_2O] donor set; in the systems with BIMA, Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA and His-BIMA, *cis*-VOL_2 can have various degrees of protonation (see Table 1 and Table 3). [d] Species characterised by the [(N_{im}, N_{im}); (N_{im}, N_{im})] donor set; in the systems with BIMA, Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA and His-BIMA, *trans*-VOL_2 can have various degrees of protonation (see Table 1 and Table 3). [e] Species characterised by the [(N_{im}, N_{im}); (N_{im}, N_{im}^{ax}); OH^-] donor set. [f] Species characterised by the [(N_{im}, N^-, NH_2); H_2O] donor set. [g] Species characterised by the [(N_{im}, N^-, NH_2); OH^-] donor set. [h] Parameters not exactly measurable for the low concentration of the species and/or the contemporaneous presence of VOL_2 and $VOLH_{-2}$. [i] Parameters not exactly measurable for the contemporaneous presence of $VOLH_{-1}$ and $VOLH_{-2}$.

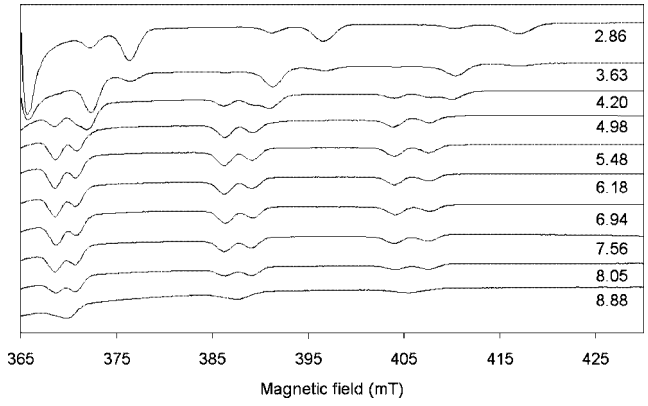
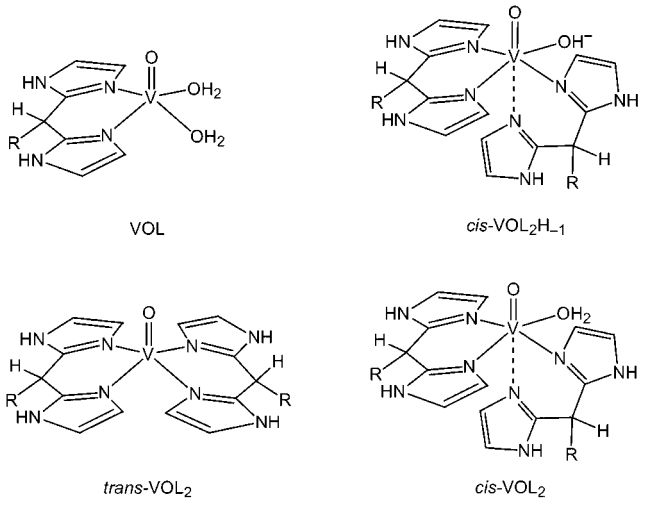


Figure 2. High field region of the X-Band anisotropic EPR spectra recorded at 140 K as a function of pH for an aqueous solution of the $V^{IV}O$/BIM system with a ligand-to-metal molar ratio of 5:1 and a $V^{IV}O$ concentration of 4 mM.



Scheme 2. Structure of the $V^{IV}O$ complexes formed by BIM (R = H), BIMA (R = NH_2), BINM (R = NO_2), Z-Gly-BIMA (R = Z-Gly) and Z-Ala-BIMA (R = Z-Ala). *Trans*-VOL_2 complex does not form with BINM, and *cis*-VOL_2H_{-1} with Z-Gly-BIMA and Z-Ala-BIMA.

bution of water to $A_\parallel$ than the other donor functions, the *cis* complex corresponds to the species with the higher $A_\parallel$ value and the *trans* to that with the lower $A_\parallel$ (Table 2). Their structure is proposed in Scheme 2. The donor set is [(N_{im}, N_{im}); (N_{im}, N_{im}^{ax}); H_2O] for the *cis*, and [(N_{im}, N_{im}); (N_{im}, N_{im})] for the *trans* isomer. Only the system with BINM constitutes an exception, since only the *cis* isomer for VOL_2 is observed.

cis-*trans* isomerism is not unusual for $V^{IV}O$ complexes and, of course, is due to the comparable stability of the two species. To date, many examples of such an isomerism have been reported in the literature.[28,29] The relative stability of the two isomers is influenced by a number of factors, including the ligand bite, the size of the chelate ring, the basicity and the steric requirements of the ligands, the hydrophobicity of the complexes; usually, large ligand bites, six-membered chelate rings, strong ligands and hydrophobicity of the complexes favour the *trans* isomer.[29,30] To the best of our knowledge, this is the first example of *cis*-*trans* isomerism with bidentate ligands forming six-membered chelate rings provided with only nitrogen donors.

In the systems with BIM, BIMA and BINM, potentiometry suggests a further deprotonation process above pH 7 and the species formed has been identified as VOL_2H_{-1}. pK values for the deprotonation of VOL_2 to give VOL_2H_{-1} fall in the range 6.97–7.76 (Table 1). As previously observed, a water molecule bound in the equatorial position of a *cis* complex with VOL_2 stoichiometry is more

acid than the bulk water,[28,30,31] and can be easily deprotonated to form the corresponding mono-hydroxo complex, *cis*-VOL_2H_{-1} or *cis*-$VOL_2(OH)$. This transformation can be followed by EPR spectroscopy, since the replacement of a water molecule with a hydroxo ion implies a marked decrease of $A_{\parallel}$. In fact, with BIM, BIMA and BINM, above pH 7.5 EPR spectra change considerably, suggesting the transformation of *cis*-VOL_2 into *cis*-VOL_2H_{-1} species (Figure 2); the decrease of the $A_{\parallel}$ value from 163.0–164.3 × 10^{-4} cm^{-1} of *cis*-VOL_2 to 159.1–161.0 × 10^{-4} cm^{-1} of *cis*-VOL_2H_{-1} (Table 2) is that expected on the basis of the "additivity rule",[26] and is similar to what has been previously observed in the literature.[30,31]

It is worth noting that Z-Gly-BIMA and Z-Ala-BIMA, even if they have a carbamide group in their structure, behave like the simple BIM, BIMA or BINM derivatives, with the only difference being that they do not form the hydroxo complex VOL_2H_{-1} (Table 1). The binding of the two bis(imidazol-2-yl)methyl moieties does not promote the deprotonation and the subsequent coordination of the (carb)amide nitrogen, unlike Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA or His-BIMA (see below); this seems to be due to the lack of a third strong donor in the ligand chain, able to close a second chelate ring after the coordination of the amide nitrogen-N^-.

Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA, His-BIMA

Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA, and His-BIMA can be considered as amino acid derivatives of BIMA, in which the carboxylic group of the amino acid forms an amide bond with the amino group of BIMA (Scheme 1).

Gly-BIMA in the fully protonated form has three titrable protons, α-Glu-BIMA and His-BIMA four (i.e. the formula is H_3L for Gly-BIMA, and H_4L for α-Glu-BIMA and His-BIMA), as reported in Table 3. The pK_a values of imidazole nitrogens are similar to those of other amino acid and peptide derivatives of the bis(imidazol-2-yl)methyl group; the highest value corresponds to the deprotonation of the ammonium group of the amino acid residue. The additional deprotonation process measured for α-Glu-BIMA and His-BIMA is due to the carboxylic group and to the imidazole nitrogen of the amino acid side-chain, respectively. The pK_a values recalculated in this work are in good agreement with those previously reported by some of the present authors.[23b,23d,23g]

For this group of ligands, the complexation scheme derived from the potentiometric and spectroscopic studies is similar to that of BIM, BIMA, BINM, Z-Gly-BIMA and Z-Ala-BIMA in the acid and neutral solution, but includes two different species at pH >7, $VOLH_{-1}$ and $VOLH_{-2}$, in which the amino and deprotonated amide group take part in the coordination. The stability constants of the complexes are presented in Table 3. The distribution curves for the $V^{IV}O$/Gly-BIMA system with a ligand-to-metal molar ratio of 5:1 are shown in Figure 3 as an example.

The EPR analysis allows us to confirm the results of the potentiometric titrations. Anisotropic EPR spectra recorded as a function of pH for the system with Gly-BIMA are displayed in Figure 4, and EPR parameters are listed in Table 2.

Table 3. Stability constants (logβ) of proton and $V^{IV}O$ complexes for Gly-BIM, α-Glu-BIMA, His-BIMA at 25.0 ± 0.1 °C and I = 0.2 M (KCl).[a]

Species	Gly-BIMA	α-Glu-BIMA	His-BIMA
H_4L		19.59(7)	20.16(3)
H_3L	16.23(1)	16.94(5)	17.58(1)
H_2L	13.19(1)	13.22(3)	13.06(1)
HL	7.79(1)	7.59(1)	7.28(1)
pK_a(Im_1)	3.04	2.65	2.58
pK_a(Im_2)	5.40	5.63	5.78
pK_a(NH_2)	7.79	7.59	7.28
pK_a(COOH)		3.72	
pK_a(Im_{His})			4.52
$VOLH_2$		17.09(2)	17.99(2)
VOLH	13.56(1)	13.51(2)	13.31(8)
VOL	8.60(3)	9.18(1)	8.76(3)
VOL_2H_4		33.18(11)	34.36(14)
VOL_2H_3		30.00(5)	
VOL_2H_2	25.49(3)	25.49(6)	24.88(13)
VOL_2H	19.17(10)		
$VOLH_{-1}$	2.12(5)	2.51(4)	2.96(4)
$VOLH_{-2}$	–4.93(4)	–4.72(3)	–5.00(8)
pK(VOL)[b]	6.48	6.67	5.80
pK($VOLH_{-1}$)[c]	7.05	7.23	7.96

[a] The uncertainties (σ values) of the protonation and stability constants are given in parentheses. [b] pK(VOL) = logβ(VOL) – logβ($VOLH_{-1}$). [c] pK($VOLH_{-1}$) = logβ($VOLH_{-1}$) – logβ($VOLH_{-2}$).

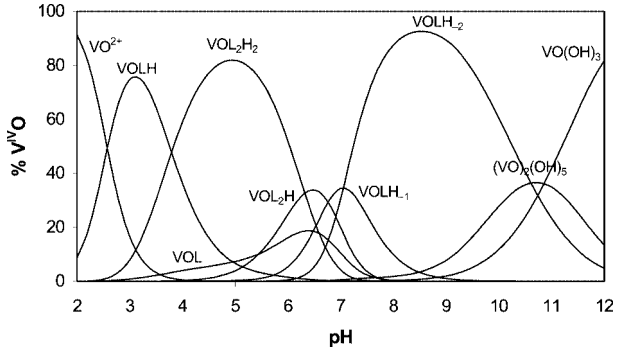


Figure 3. Species distribution for the $V^{IV}O$/Gly-BIMA system as a function of pH with a ligand-to-metal molar ratio of 5:1 and a $V^{IV}O$ concentration of 1 mM.

In all the systems we can identify two mono-chelated species with the compositions VOLH and VOL, with similar EPR parameters, $A_{\parallel}$ = 168.7–170.3 × 10^{-4} cm^{-1}, and equatorial donor set [(N_{im}, N_{im}); H_2O; H_2O]; the only difference is the protonation of the terminal amino group, $–NH_3^+$ in VOLH and $–NH_2$ in VOL. For α-Glu-BIMA and His-BIMA, the additional species $VOLH_2$ has the carboxylate or the imidazole nitrogen of the amino acid residue protonated.

At excess of ligand, a number of VOL_2H_x (with x = 1–4) complexes predominate if pH >4 (Table 3). They are characterised by the same donor set and a *cis*-*trans* isomer-

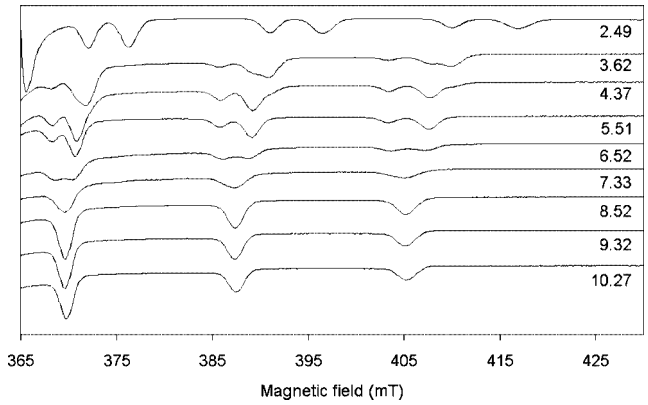


Figure 4. High field region of the X-Band anisotropic EPR spectra recorded at 140 K as a function of pH for an aqueous solution of the $V^{IV}O$/Gly-BIMA system with a ligand-to-metal molar ratio of 5:1 and a $V^{IV}O$ concentration of 4 mM.

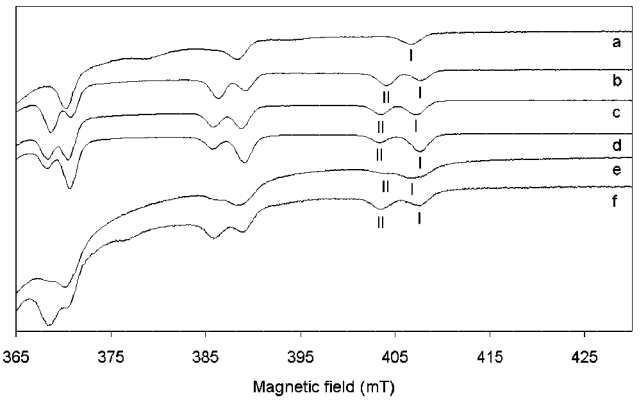


Figure 5. High field region of the X-Band anisotropic EPR spectra of the bis-chelated complexes formed by BINM, BIM, BIMA, GlyBIMA, α-Glu-BIMA and HisBIMA recorded in aqueous solutions at 140 K with a $V^{IV}O$ concentration of 4 mM: a) BINM: L/M = 1, pH = 7.20; b) BIM: L/M = 5, pH = 6.95; c) BIMA: L/M = 5, pH = 6.60; d) Gly-BIMA: L/M = 5, pH = 5.50; e) α-Glu-BIMA: L/M = 3, pH = 5.65; f) HisBIMA: L/M = 3, pH = 6.60. I and II denote *cis* and *trans* species, respectively.

ism similar to that discussed for BIM, BIMA, BINM and Z-Gly-BIMA (Table 2). The difference is the protonation degree of the ligands (for example, VOL_2H_2 and VOL_2H species formed by Gly-BIMA have two and one non-coordinating amino group protonated, respectively). Analogously to the previous systems, the *cis* complexes are characterised by a higher $A_{\parallel}$ value ($A_{\parallel}$ = 163.7–165.2 × 10^{-4} cm^{-1}) and a [(N_{im}, N_{im}); (N_{im}, N_{im}^{ax}); H_2O] donor set, whereas the *trans* species shows lower $A_{\parallel}$ values ($A_{\parallel}$ = 158.2–158.4 × 10^{-4} cm^{-1}), as expected on the basis of the "additivity rule",[26] and a [(N_{im}, N_{im}); (N_{im}, N_{im})] donor set. The relative amount of the two isomers does not change in the pH range 4–7 for a given ligand, but it can vary depending on the ligand; in particular, the relative amount of the *cis* isomer with respect to the *trans* increases in the order: His-BIMA < Gly-BIMA < α-Glu-BIMA ≈ α-Asp-BIMA.

In Figure 5 a comparison between the EPR spectra for a number of bis-chelated complexes formed by bis(imidazol-2-yl)methyl ligands is shown. As mentioned above, some of the present authors recently demonstrated that for ligands with the same bite, basicity and size of the chelate ring, the hydrophilicity of the complexes is the critical factor in determining the relative amount of the *cis* and *trans* species in water; particularly, hydrophilic complexes prefer the *cis* arrangement.[29] This could also explain the results displayed in Figure 5: the hydrophilic bis-chelated complexes formed by BIMA, Gly-BIMA, α-Glu-BIMA and His-BIMA prefer *cis* arrangement, whereas the most hydrophobic complex formed by BIM prefer the *trans* one. With this rule in mind, the reason for which BINM forms only a *cis* bis-chelated complex can be rationalised: BINM is the most hydrophilic ligand, because of the presence of a formal positive charge on the nitrogen and a formal negative charge on one of the oxygen atoms for each of the two $–NO_2$ groups.

Differently from the BIM, BIMA, BINM, Z-Gly-BIMA and Z-Ala-BIMA systems, above pH 7 the formation of two new species, with the composition $VOLH_{-1}$ and $VOLH_{-2}$, is observed. These species cannot be confused at all with the hydroxo complexes VOL_2H_{-1} present in the previously examined systems because they exist in a wider pH range and are characterised by a higher intensity of the EPR signals, indicating a different coordination mode. Moreover, the formation of these complexes is accompanied by a new absorption maximum in the UV/Vis spectra around 390 nm, as demonstrated by an examination of Figure 6, where the distribution curves of $V^{IV}O$/His-BIMA species and the variation of molar absorptivity of the system at 386 nm are depicted as a function of pH. The appearance of this new band suggests the coordination of a "strong" donor atom, as a consequence of the deprotonation and coordination of the amide nitrogen. Similar changes in the electronic spectra were observed in the case of the $V^{IV}O$/SalGly system (SalGly = salicylglycine), where simultaneously to the deprotonation and coordination of the amide-N^- a new absorption band is observed around 400 nm.[21f]

For Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA and His-BIMA, in contrast with Z-Gly-BIMA and Z-Ala-BIMA, the presence of a terminal amino group allows the deprotonation and coordination of the amide nitrogen, with the closure of two five-membered chelate rings; this possibility results in the formation of $VOLH_{-1}$ and $VOLH_{-2}$ with [(N_{im}, N^-, NH_2); H_2O] and [(N_{im}, N^-, NH_2); OH^-] donor sets. Their structure is represented in Scheme 3. As noted above, with Z-Gly-BIMA and Z-Ala-BIMA, the second chelate ring does not form because the amino group is involved in a "carbamate-like" bond with the benzyloxycarbonyl group. For α-Asp-BIMA and α-Glu-BIMA, the formation of the final species $VOLH_{-2}$ takes place at higher pH values with respect to Gly-BIMA and His-BIMA, probably because of the presence of a negative charge on the carboxylate group which prevents the deprotonation of the amide nitrogen.

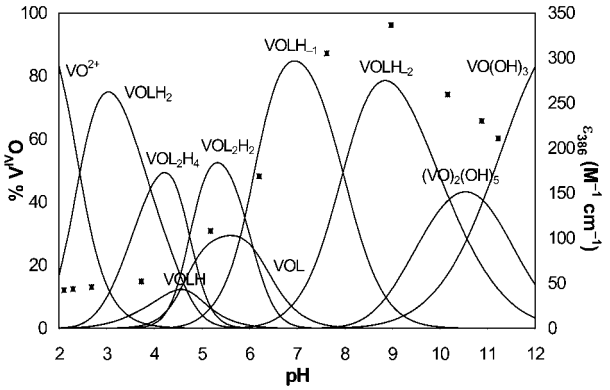
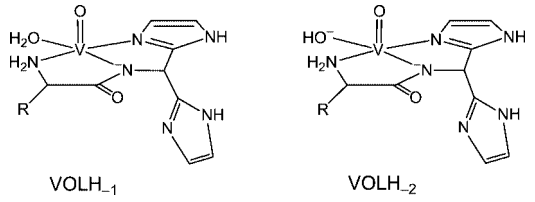


Figure 6. Species distribution for the $V^{IV}O$/His-BIMA system as a function of pH with a ligand-to-metal molar ratio of 4:1 and a $V^{IV}O$ concentration of 1 mM. The superimposed squares show the variation of molar absorptivity ε at 386 nm.



Scheme 3. Structure of the $VOLH_{-1}$ and $VOLH_{-2}$ complexes formed by Gly-BIMA (R = H), α-Asp-BIMA (R = CH_2COO^-), α-Glu-BIMA (R = $CH_2CH_2COO^-$) and His-BIMA (R = 4-CH_2-imidazole).

Since Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA and His-BIMA display a comparable complexing scheme, this allows us to rule out the participation of the side-chain of α-Asp, α-Glu or His amino acids to the coordination.

As a final comment, we propose some observations on the differences between the behaviour at basic pH values of BIM, BIMA, BINM, Z-Gly-BIMA and Z-Ala-BIMA which form *cis*-VOL_2H_{-1} on the one hand, and Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA, His-BIMA which form $VOLH_{-2}$ on the other hand: (i) *cis*-VOL_2H_{-1} undergoes hydrolytic reactions to give $[(VO)_2(OH)_5]^-$ and $[VO(OH)_3]^-$ above pH 9, whereas $VOLH_{-2}$ exists in a rather wide pH range (7.0–11.0), suggesting the coordination of stronger donors like the deprotonated amide nitrogen; (ii) UV/Vis electronic absorption spectra recorded at pH >7 on equimolar solutions of $V^{IV}O$ ions and His-BIMA are characteristic of a limpid solution: this allows us to rule out the presence of a 1:2 complex, which should result in the precipitation of the remaining part of the $V^{IV}O$ ion as $VO(OH)_2$, and supports the formation of 1:1 species like $VOLH_{-1}$ and $VOLH_{-2}$; (iii) the linewidth of the EPR signal due to $VOLH_{-2}$ is notably narrower than *trans*-VOL_2, indicating a lower number of nitrogen atoms coordinated (three instead of four): indeed, the nitrogen atoms on the equatorial plane increase the linewidth of the EPR signal because of the superhyperfine coupling between the unpaired electron on the $V^{IV}O$ ion and the ^{14}N nucleus (I = 1).

Density Functional Calculations of the $VOLH_{-1}$ and $VOLH_{-2}$ Structures

An optimised geometry of the $VOLH_{-1}$ and $VOLH_{-2}$ complexes formed by Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA and His-BIMA was calculated by performing Density Functional Theory (DFT) calculations with the Gaussian 03 program.[32] In the last few years, there has been growing use of DFT methods because they give rather good results in the optimisation of the geometries of transition-metal complexes.[33] The functional B3LYP,[34,35] which has been demonstrated to yield good agreement with the experimental structures for many vanadium compounds,[33d,36] and the mixed basis set 6-311g for vanadium and 6-31g(d) for the other elements were used. With this latter set, differences of 0.023 Å in V–C and 0.010 Å in C–O bond lengths are obtained for $[V(CO)_6]^-$ and of 0.001 Å in Cr–C and 0.009 Å in C–O distances for $[Cr(CO)_6]$.[36a]

Attempts to simulate the structure of $VOLH_{-1}$ and $VOLH_{-2}$ complexes with the second imidazole ring coordinated in the axial position, in *trans* to the oxo group of the V=O unit, were unsuccessful. Therefore, in order to speed up the calculation time, we simulated the structure of $VOLH_{-1}$ and $VOLH_{-2}$ by replacing one imidazole ring with a hydrogen atom and abbreviating with Gly-IMA the obtained ligand *N*-glycyl-(imidazol-2-yl)methylamine. The results are listed in Table 4. The structure of the $VOLH_{-2}$ complex with Gly-IMA, simulated with the mixed 6-311g/6-31g(d) basis set, is displayed in Figure 7.

From an examination of Table 4 it can be noticed that beginning from the 6-31g basis set comparable results are obtained, suggesting that also simple sets can provide a satisfactory agreement with a real structure, whereas more complete basis sets supply only a marginal improvement in the geometric parameters. The distance of V=O(oxo) bond ranges were between 1.588 and 1.622 Å, that of V–N(amino) between 2.150 and 2.163 Å, that of V–N^-(amide) between 2.009 and 2.021 Å, that of V–N(imidazole) between 2.112 and 2.140 Å and that of V–O(hydroxo) between 1.860 and 1.882 Å.[37] An important structural parameter, which will be used for estimating the $A_\parallel$ value for $VOLH_{-1}$ and $VOLH_{-2}$ species, is the dihedral angle θ, defined by the vanadyl oxo, the vanadium atom, the coordinated imidazole N and the carbon atom that bridges the two imidazole nitrogen atoms.[27,38] From an examination of Table 4, it can be noticed that it falls in the range 111.1–112.8°, suggesting an almost perpendicular arrangement of the imidazole ring with respect to the V=O bond.[27,38] The structural data of our simulations are comparable with those of the [VO(Gly-L-Val)(phen)]·H_2O complex (see Table 4), characterised by a similar equatorial donor set: [(NH_2, N^-, COO^-); (N_{pyr}, N_{pyr}^{ax})].[21] A shorter V–O(hydroxo) distance (1.785 Å) has been measured for the complex *cis*-[VO(OH)(4,4′-dtbipy)$_2$]-BF_4·1.2H_2O (Table 4).[36c] We have no explanation for this.

For the complex $VOLH_{-1}$, simulated with Gly-IMA with a water molecule replacing the OH^- ion, bond lengths of 1.567, 2.155, 1.948, 2.091 and 2.130 Å are obtained for V=O(oxo), V–N(amino), V–N^-(amide), V–N(imidazole)

Table 4. Details and structural parameters of the DFT calculations on [VO(Gly-IMAH$_{-1}$)(OH)] and [VO(Gly-IMAH$_{-1}$)(H_2O)]$^+$ and comparison with similar species reported in the literature.[a]

Complex	Basis set	Basis functions	V=O	V–N(amino)	V–N$^-$(amide)	V–N(aromatic)	V–O[b]	Dihedral angle θ[c]
[VO(Gly-IMAH$_{-1}$)(OH)]	3-21g	166	1.609	2.140	1.985	2.077	1.839	109.94
[VO(Gly-IMAH$_{-1}$)(OH)]	6-31g	166	1.617	2.150	2.009	2.118	1.868	111.59
[VO(Gly-IMAH$_{-1}$)(OH)]	6-31g(d)	171	1.589	2.163	2.017	2.139	1.862	111.87
[VO(Gly-IMAH$_{-1}$)(OH)]	6-31g+	231	1.622	2.156	2.010	2.112	1.882	111.11
[VO(Gly-IMAH$_{-1}$)(OH)]	6-311g	238	1.609	2.158	2.017	2.115	1.864	112.14
[VO(Gly-IMAH$_{-1}$)(OH)]	6-311g for V/ 6-31g(d) for C,H,N,O	241	1.588	2.163	2.021	2.140	1.860	112.76
[VO(Gly-IMAH$_{-1}$)(H_2O)]$^+$	6-311g for V/ 6-31g(d) for C,H,N,O	243	1.567	2.155	1.948	2.091	2.130	105.85
[VO(Gly-L-Val)(phen)] [d]			1.587	2.158	1.978	2.155		
cis-[VO(OH)(4,4′-dtbipy)$_2$]$^+$ [e]			1.659			2.134 [f]	1.785	

[a] Gly-IMA is *N*-glycyl-(imidazol-2-yl)methylamine. [b] O belonging to an OH^- ion or to a H_2O molecule. [c] Defined by the vanadyl oxo, the vanadium atom, the coordinated imidazole nitrogen and the carbon atom that bridges the two imidazole nitrogens.[27,38] [d] [VO(Gly-L-Val)(phen)]·H_2O, where Gly-L-Val is glycyl-L-valinato and phen is 1,10-phenanthroline.[21l] [e] *cis*-[VO(OH)(4,4′-dtbipy)$_2$]-BF_4·1.2H_2O, where 4,4′-dtbipy is 4,4′-di-*tert*-butyl-2,2′-bipyridine.[36c] [f] Mean values.

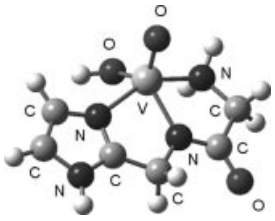


Figure 7. Simulated structure of the complex [VO(Gly-IMA)(OH)] calculated by the DFT method using the 6-311g basis set for vanadium and 6-31g(d) for the other elements (see Table 4). Gly-IMA is *N*-glycyl-(imidazol-2-yl)methylamine.

and V–O(water), respectively.[39] The dihedral angle θ is 105.9° (Table 4).[39] As expected, V–N$^-$(amide) becomes shorter as the length of the bond in the *trans* position increases; thus, V–N$^-$(amide) in VOLH$_{-1}$ is shorter than in VOLH$_{-2}$ (1.948 vs. 2.021 Å)[39] because H_2O replaces the OH^- ion.

Effect of the V–N$^-$(amide) Bond on the $A_\parallel$ Value

By continuing the discussion of a previous work,[20] we would now analyse the bond between a deprotonated amide-N$^-$ and a vanadyl ion and its effect on the ^{51}V anisotropic parallel hyperfine constant of $V^{IV}O$ complexes. The latter is indicated with $A_\parallel$ or A_z, depending on the symmetry of the complexes, axial or rhombic (here we consider only axial species with two g, $g_\parallel$ and $g_\perp$, and two A, $A_\parallel$ and $A_\perp$, values). For the ^{51}V nucleus, $A_\parallel$ can be expressed as shown in Equation (2).[40]

$$A_{\parallel} = P_d\left[\beta^2\left(-\kappa-\frac{4}{7}\right)+(g_{\parallel}-2.0023)+\frac{3}{7}(g_{\perp}-2.0023)\right] \quad (2)$$

In this equation $P_d = g_N\beta_N g\beta\langle r^{-3}\rangle$ is the dipolar interaction between the unpaired electron and the ^{51}V nucleus and is determined by the spatial distribution of the *d* electron,[40] κ is the Fermi contact term and measures the unpaired *s*-electron spin density at the nucleus, and β^2 is, to a good approximation, the population of the ground state *d* orbital containing the unpaired spin (for $V^{IV}O$ species with C_{2v} symmetry or higher, it measures the population of the d_{xy} orbital). Pecoraro assumed the terms κ and P_d as constants and reported a value of 0.85 for κ and of 128×10^{-4} cm^{-1} for P_d.[38] A similar value for P_d (125×10^{-4} cm^{-1}) has been used by Deligiannakis and Kabanos.[21h] Mabbs and Collison report a significantly higher value (173.5×10^{-4} cm^{-1}).[41]

In the "additivity rule",[26] Chasteen estimated $A_\parallel$ or A_z of a $V^{IV}O$ species from the contribution of each of the four equatorial donor groups, see Equation (1).[26] The contribution of the various groups to $A_\parallel$ is listed in Table 5.

The rule provides a valid criterion for the identification of the equatorial donor atoms. Additions or corrections concerning the contribution of N(imino),[20] Cl^- and SCN^-,[21j] CO(carbonyl)[42] and COO^-,[21m] appeared subsequently in the literature. Pecoraro and co-workers proposed that for imidazole the overlap of the π orbitals of the aromatic ring with the d_{xy} vanadium atomic orbital bearing the unpaired electron would increase the covalence of the metal–ligand bond and produce a decrease of the β^2 value and of the contribution of an imidazole nitrogen to $A_\parallel$, see Equation (2).[27,38] They determined an empiric equation to calculate the value of $A_\parallel$(imidazole) as a function of the dihedral θ angle, see Equation (3) where $x = 42.72\times10^{-4}$ cm^{-1} and $y = 2.96\times10^{-4}$ cm^{-1}.[27,38]

$$A_\parallel(\text{imidazole}) = x + y\sin(2\theta - 90) \quad (3)$$

With the data reported in Table 5, an expected value of $A_\parallel$ for the complexes VOLH$_{-1}$ and VOLH$_{-2}$ formed by Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA and His-BIMA can be calculated. The values of 32.7×10^{-4} cm^{-1} and 35.3×10^{-4} for $A_\parallel$(amide) in VOLH$_{-1}$ (total equatorial charge of –1, Table 5) and VOLH$_{-2}$ (total equatorial charge of –2, Table 5), and of 45.2×10^{-4} and 44.8×10^{-4} cm^{-1} for $A_\parallel$(imidazole) in VOLH$_{-1}$ and VOLH$_{-2}$ calculated with the dihe-

dral θ angles obtained from DFT simulations (Table 4) were used.[39] $A_{\parallel}$ of 163.6×10^{-4} cm^{-1} for $VOLH_{-1}$ and 158.9×10^{-4} cm^{-1} for $VOLH_{-2}$ are derived, comparable to the experimental ones (Table 2).

Table 5. Contribution of the various groups to ^{51}V hyperfine coupling constants $A_{\parallel}$.[a]

Donor group[b]	Contribution to $A_{\parallel}$[c]	Ref.
H_2O	45.6	[26]
COO^-	42.1	[21m]
CO	43.5	[42]
OH^-	38.7	[26]
$O_{aromatic}^-$ (O_{ar}^-)	38.9	[26]
RO^-	35.3	[26]
$S_{aromatic}^-$ (S_{ar}^-)	35.3	[26]
RS^-	31.9	[26]
NH_2	40.1	[26]
N_{imino}	41.6	[20]
$N_{imidazole}$ (N_{im})	$42.72 + 2.96 \cdot \sin(2\theta - 90)$[d]	[27,38]
$N_{pyridine}$ (N_{pyr})	40.7	[26]
N_{amide} (N^-)	32.7 (–1), 35.3 (–2), 38.6 (–3), 40.9 (–4)[e]	[20]
Cl^-	44.2	[21j]
SCN^-	43.2	[21j]

[a] Contribution measured in 10^{-4} cm^{-1}. [b] Between round brackets are given the symbols used in Table S1 of the electronic supporting information and in other parts of the text. [c] In many parts of the text the contribution of each donor group to $A_{\parallel}$ is also indicated with $A_{\parallel}$(donor). [d] θ is the dihedral angle defined by the vanadyl oxo, the vanadium atom, the coordinated imidazole nitrogen and the carbon atom that bridges the two imidazole nitrogen atoms.[27,38] [e] Between round brackets, the total charge present in the equatorial plane of the $V^{IV}O$ ion (including that of the amide nitrogen).

Concerning the amide contribution to $A_{\parallel}$, $A_{\parallel}$(amide), it was found to be sensitive to the total charge of the donor atoms in the equatorial plane; in particular, its value decreases with a decrease in the total equatorial charge.[20,21b,21h] By taking into account the $A_{\parallel}$(amide) values for 37 $V^{IV}O$ compounds with a V–N$^-$(amide) bond, we recently calculated 35.5, 38.3 and 40.9×10^{-4} cm^{-1} for the contribution to $A_{\parallel}$ when the total equatorial charge is –4, –3 or –2 (including that of the amide nitrogen) and by extrapolation 32.7×10^{-4} cm^{-1} for the –1 equatorial charge (Table 5),[20] in good agreement with the results of Tasiopoulos et al.[21h]

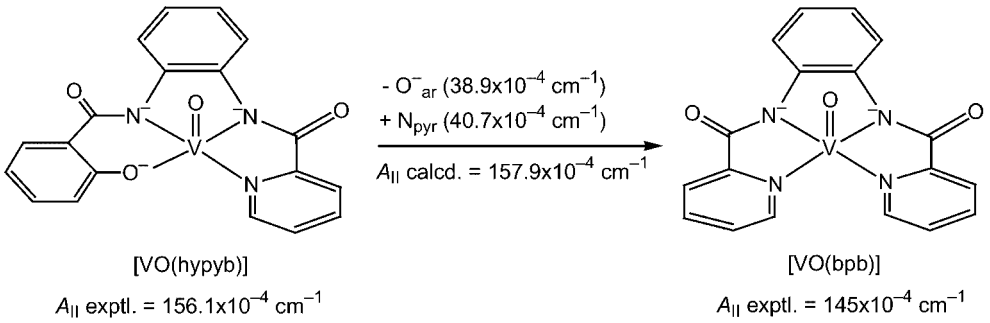
On the basis of the methods reported in the literature for rationalising some cases of anomalous EPR behaviour displayed by $V^{IV}O$ complexes, three different hypotheses could be advanced to explain the unusual reduction of $A_{\parallel}$(amide) with the total equatorial charge:

(i) Two limit resonance structures for a deprotonated amide group coordinated through nitrogen, one "amide-like" with the nitrogen atom negatively charged and a double bond between the carbon and oxygen atoms of the carbonyl group, and another "imine-like" with the carbonyl oxygen negatively charged and a double bond between the carbon and nitrogen atoms, can be assumed.[21b] With a decrease in the total equatorial charge around vanadium the importance of the "amide-like" arrangement should increase, to which a lower $A_{\parallel}$(amide) contribution corresponds.[21b] This explanation would result in a change in C–N, C=O and V–N distances as a function of $A_{\parallel}$(amide), but is not supported by the data of the structures resolved through a single-crystal X-ray diffraction analysis for which EPR parameters are reported.[20]

(ii) A reduction of the P_d parameter, which should decrease the electron density on the metal ion and hence the V=O bond length, could be proposed. A similar explanation was put forward by Kabanos and co-workers to explain the reduction of $A_{\parallel}$ by about 10%, relative to the value predicted with the "additivity rule", for the complexes [VOX(capca)], where Hcapca is *N*-{2-[(2-pyridylmethylene)amino]phenyl}pyridine-2-carboxamide and X^- is an anion (Cl^-, SCN^-, CH_3COO^- or $PhCOO^-$) occupying the axial position.[21j] This mechanism can be ruled out for $V^{IV}O$ complexes involving a V–N$^-$(amide) bond, because no correlation between the $A_{\parallel}$(amide) values and V=O length is observable.[20] According to the theoretic treatment of Mabbs and Collison,[41] to Pecoraro and co-workers[27,38] and to a previous paper of Deligiannakis and Kabanos,[21h] we believe that the value of P_d can be assumed to be constant.

(iii) An overlap between the π orbitals of the ligand and d_{xy} atomic orbital of vanadium, which increases the covalence of the V–N$^-$(amide) bond and decreases β^2 and $A_{\parallel}$ values [see Equation (2)] could be suggested, i.e. a mechanism similar to that proposed by Pecoraro and co-workers to justify the reduction of $A_{\parallel}$(imidazole) when the aromatic ring is perpendicular to the V=O group.[27,38] However, this possibility is not applicable to the V–N$^-$(amide) bond if the amide group remains perpendicular to the V=O group, because the delocalised π system is not in a favourable position to overlap with the d_{xy} orbital.

The question arising is: why only the V–N$^-$(amide) bond (and not the other V-donor bonds) should compensate a lower electronic density in the equatorial plane of a $V^{IV}O$ complex through an increase of the covalence? In order to evaluate the effect of the total equatorial charge on $A_{\parallel}$, we re-analysed the EPR parameters of the structures containing a V–N$^-$(amide) bond (see Table S1 in the electronic supporting information). We compared several couples of $V^{IV}O$ structures, in which the only variable is the equatorial charge; in particular, we examined four couples which only differ in one donor and in one unit of the total equatorial charge (two couples with –4/–3 and two with –3/–2 equatorial charge), two couples which differ in one donor but two units of equatorial charge (–4/–2) and, for comparison, six couples which differ in one donor but not in equatorial charge (two couples with –4/–4, two with –3/–3 and two with –2/–2). To avoid taking into account the influence of the donor which changes going from higher to lower equatorial charge, for each couple we considered the experimental $A_{\parallel}$ value ($A_{\parallel}$ exp.) for the complex with higher equatorial charge and, from it, calculated $A_{\parallel}$ ($A_{\parallel}$ calcd.) for the complex with lower charge by subtracting the contribution of the donor which is replaced and adding that of the donor which replaces it (indicated in bold in Table S1 of Supporting Information), with the contribution of several donors taken from Table 5.[43] If $A_{\parallel}$ was only dependent on the do-



Scheme 4. Methods for calculating $A_{\parallel}$ ($A_{\parallel}$ calcd.) for a $V^{IV}O$ complex containing a V–N^{-}(amide) bond from the experimental $A_{\parallel}$ value ($A_{\parallel}$ exp.) of the species with higher total equatorial charge. H_3hypyb = 1-(2-hydroxybenzamido)-2-(2-pyridinecarboxamido)benzene,[21e] and H_2bpb = 1,2-bis(2-pyridinecarboxamido)benzene.[21i]

nor functions bound to the $V^{IV}O$ ion and not on the equatorial charge, we should expect an almost exact coincidence between $A_{\parallel}$ calcd. and $A_{\parallel}$ exp. for the species with lower charge; every difference between the two values can be attributable only to the decrease of the equatorial charge. This is illustrated in Scheme 4.

The conclusion is that the decrease of the equatorial charge always results in a decrease of the $A_{\parallel}$ value for a $V^{IV}O$ complex, whereas if the equatorial charge remains the same no significant changes in the $A_{\parallel}$ value can be observed. In particular, in the two couples with –4/–3 equatorial charge, in the two with –3/–2 and in the two with –4/–2 a reduction in the range 3.0–3.8, 3.2–8.9 and 7.6–10.2% is observed, respectively; on the other hand, in the six couples with the same equatorial charge the maximum difference (negative or positive) is 1.2%. It is worth noting that the most marked reduction is observed when changing the equatorial charge from –4 to –2. The comparison between the $VOLH_{-2}$ complex studied in this work (total equatorial charge of –2) and two $V^{IV}O$ species with a charge of –3 and –2 follows the same trend.

It is obvious that, if the contribution to $A_{\parallel}$ of all the donor functions is considered constant, the decrease in $A_{\parallel}$ for $V^{IV}O$ complexes containing a V–N^{-}(amide) bond must be entirely attributed to the decrease of $A_{\parallel}$(amide). However, analysing the 14 couples of $V^{IV}O$ complexes in Table S1 of the electronic supporting information, the hypothesis that all the donors participate in the reduction of $A_{\parallel}$ could be advanced, i.e. all the contributions of the four equatorial donors could decrease with a decrease in the total equatorial charge. Of course, this reduction can be almost negligible; for example, in the couple **I** in Table S1 of the supporting information it is enough if the contribution of every donor to $A_{\parallel}$ decreases by 3.0% to obtain an agreement with the calculated value, i.e. the contribution of phenolate (O_{ar}^{-}) will be of 37.7×10^{-4} cm^{-1} instead of 38.9×10^{-4} cm^{-1}. This effect is not evident when bis-chelated complexes of bidentate ligands (often with the same donor function),[44] like those analysed by Chasteen in formulating the "additivity rule", are considered.[26] However, this difference falls within the uncertainty of ca. 3×10^{-4} cm^{-1} for the $A_{\parallel}$ value estimated by Chasteen and Pecoraro.[26,27] Therefore, we would stress that the "additivity rule" is respected; what should be taken into account in its application is that the contribution of the various donor functions could vary in a narrow range, probably centred around the value reported in Table 5, depending on the type of $V^{IV}O$ complex under examination.

Since the κ and probably P_d terms can be considered constant for vanadyl complexes,[21h,38,41] a reduction of $A_{\parallel}$ could be only connected to a reduction of coefficient β^2 in Equation (2). By following the discussion of Ballhausen and Gray, in a square pyramidal $V^{IV}O$ complex the d_{xy} atomic orbital with b_{2g} symmetry which bears the unpaired electron can covalently interact with the ligand orbitals only through a π bond, see Equation (4).[45]

$$\psi(b_{2g}) = \beta d_{xy} + (\gamma_1\pi_{x1} + \gamma_2\pi_{y2} - \gamma_3\pi_{x3} - \gamma_4\pi_{y4}) \quad (4)$$

where β is the coefficient of the d_{xy} vanadium atomic orbital, see Equation (2), and γ_i are the coefficients of the ligand orbitals π_i with suitable symmetry to overlap with d_{xy}.[46] A value of 1 for β^2 indicates that the unpaired electron is localised exclusively on the vanadium d_{xy} orbital and that there is no delocalisation onto the ligands; on the other hand, a value of β^2 lower than 1 indicates that a $(1–\beta^2)$ fraction of the spin density is delocalised onto the ligands, causing a decrease of $A_{\parallel}$ value through Equation (2).

By analysing the data reported in Table S1 of the electronic supporting information, we think that it can not be excluded that the reduction of $A_{\parallel}$ is due to an increase of the covalence of all or part of the four equatorial V-donor bonds through a π interaction between the d_{xy} orbital of vanadium and the π wavefunction of the ligands with b_{2g} symmetry in the C_{4v} group (for example, p atomic orbitals of oxygen in $O_{aromatic}^{-}$, RO^{-}, OH^{-}, COO^{-}, and of sulfur in $S_{aromatic}^{-}$, RS^{-}, or π aromatic orbitals of phenols, thiols, imidazole and pyridine rings, imino groups with suitable orientation to overlap with the d_{xy} orbital). Probably, such a π interaction is necessary when the total equatorial charge around vanadium diminishes and the four σ bonds are not sufficient to neutralise the +2 charge of the vanadyl ion. We do not believe that the decreased contribution of the deprotonated N^{-}(amide) function to $A_{\parallel}$ is the only reason for the decrease in $A_{\parallel}$. Further studies are, however, necessary to clarify this topic.

Conclusions

Simple amino acid derivatives of bis(imidazol-2-yl)-methylamine coordinate the $V^{IV}O$ ion at acid pH values and keep it in solution until the deprotonation and the coordination of the amide group occurs. A ligand-to-metal molar ratio between 3:1 and 5:1 is enough to avoid the hydrolysis of $V^{IV}O$ solutions; on the other hand, for ligands with weaker anchoring groups higher ratios are required: for example 10:1 for HisGlyGly provided with the (NH_2, CO, N_{im}^{ax}) donor set,[21o] and 15:1 for GlyGlyHis and GlyGlyCys with the (COO^-, CO) set.[21o] This suggests that the bis(imidazol-2-yl)methyl residue is an anchoring group of intermediate strength, weaker than phenolate-O^- or thiolate-S^- but stronger than amino-NH_2 or carboxylate-COO^-.

The presence of a free terminal amino group seems to be a necessary condition to promote the deprotonation of the amide bond through the closure of a second chelate ring besides that formed by imidazole and deprotonated amide nitrogens; its absence, like with Z-Gly-BIMA and Z-Ala-BIMA, stops the complexation to the VOL_2 complex.

The identical complexing behaviour of Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA and His-BIMA indicates that the side-chain of the α-Asp, α-Glu or His residues does not take part in the coordination. This is not too surprising because the carboxylate group of α-Asp-BIMA and α-Glu-BIMA should close seven- and eight-membered chelate rings, and the imidazole nitrogen of His-BIMA a seven-membered ring. Moreover, the lower affinity of the $V^{IV}O$ ion for nitrogen atoms with respect to Cu^{II} hinders the formation of the dinuclear structures observed for α-Asp-BIMA,[23g] α-Glu-BIMA[23g] and His-BIMA.[23b]

Also with Gly-BIMA, α-Asp-BIMA, α-Glu-BIMA and His-BIMA the "additivity rule" for calculating the ^{51}V anisotropic parallel hyperfine coupling constant ($A_\parallel$) is followed,[20,21j,21m,26,27,38,42] but only attributing a reduced contribution to $A_\parallel$(amide) when the total equatorial charge around the vanadyl ion decreases.[20,21b,21h] This simplification allows us to obtain a good agreement between the calculated and experimental $A_\parallel$ values,[20,21o] but is justified only if the contribution of all the other donors is considered constant so that the reduction of $A_\parallel$ can be entirely attributed to a reduction of $A_\parallel$(amide). In this work we present the new idea that all four equatorial donors could contribute to reducing the positive charge of the vanadyl ion when a decrease in the total equatorial charge is considered; the mechanism could be based on an increase of the covalence of V-donor bonds through π interactions involving the overlap of the ligand orbitals with d_{xy} bearing the unpaired electron, which in turn results in a decrease of the $A_\parallel$ value, according to Equation (2). However, further experimental data must be collected to confirm this hypothesis.

Experimental Section

Syntheses: The synthetic procedures for preparation of simple amino acid derivatives containing the bis(imidazoly-2-yl)methyl moiety have already been reported.[23b,47] The purities of products were checked by ^1H NMR and concentrations were determined by potentiometric titration. $V^{IV}O$ solutions were prepared following literature methods.[48]

Potentiometric Measurements: The stability constants of proton and $V^{IV}O$ complexes were determined by pH-potentiometric titrations on 3–10 mL of samples. The ligand-to-metal molar ratio was between 1:1 and 5:1 and $V^{IV}O$ concentration was 0.001–0.004 M. Titrations were performed from pH 2.0 until precipitation or very extensive hydrolysis by adding carbonate-free KOH of known concentration (ca. 0.2 M KOH).[49] The pH was measured with a Metrohm 6.0234.100 combined electrode, calibrated for hydrogen concentration by the method of Irving et al.[50] Measurements were carried out at 25.0 ± 0.1 °C and at a constant ionic strength of 0.2 M KCl with a Radiometer ABU91 automatic titration system or MOLSPIN pH-meter equipped with a digitally operated syringe (1.00 mL) controlled by a computer. Purified argon was bubbled through the samples to ensure the absence of oxygen. The number of experimental points was 50–100 for each titration curve and the reproducibility of the points included in the evaluation was within 0.005 pH units in the whole pH range examined. The stability of the complexes, reported as the logarithm of the overall formation constant $\beta_{pqr} = [VO_pL_qH_r]/[VO]^p[L]^q[H]^r$, where VO stands for the $V^{IV}O$ ion, L is the deprotonated form of the ligand and H is the proton, was calculated with the aid of the SUPERQUAD[51] and PSEQUAD programs.[52] Standard deviations were calculated by assuming random errors. Conventional notation was used: negative indices for protons indicate either the dissociation of groups which do not deprotonate in the absence of $V^{IV}O$ coordination, or hydroxo ligands. Hydroxo complexes of $V^{IV}O$ were taken into account and the following species were assumed: $[VO(OH)]^+$ ($\log\beta_{10-1} = -5.94$), $[(VO)_2(OH)_2]^{2+}$ ($\log\beta_{20-2} = -6.95$), with stability constants calculated from the data of Henry et al.[53] and corrected for the different ionic strengths by use of the Davies equation,[54] $[VO(OH)_3]^-$ ($\log\beta_{10-3} = -18.0$) and $[(VO)_2(OH)_5]^-$ ($\log\beta_{20-5} = -22.0$).[55]

Spectroscopic Measurements: Anisotropic EPR spectra were recorded for aqueous solutions with an X-band (9.35 GHz) Bruker EMX spectrometer in the temperature range 120–140 K. As usual for low temperature measurements, a few drops of DMSO were added to the samples to ensure good glass formation. The spectra were simulated with the computer program Bruker WinEPR SimFonia.[56] Although the temperature is different during the potentiometric and EPR measurements, according to the data in the literature the same stoichiometry and coordination mode of the main species can be supposed.[19] Electronic spectra were recorded with Perkin–Elmer Lambda 25 or 35 spectrophotometers in the same concentration range as used for potentiometry. All operations were performed under a purified argon atmosphere in order to avoid oxidation of the $V^{IV}O$ ion.

Computational Details: All calculations presented in this paper were performed using the Gaussian 03 program (revision C.02)[32] and DFT methods.[57] The hybrid exchange-correlation functional B3LYP was employed.[34,35] Several basis functions were used for the calculations: 3-21g, 6-31g, 6-31g(d), 6-31+g, 6-31g(d,p) and 6-311g; finally, the mixed set with 6-311g for vanadium and 6-31g(d) for the other elements was chosen. Full geometry optimisations were carried out on the $VOLH_{-1}(H_2O)$ and $VOLH_{-1}(OH)$ complexes (i.e. $VOLH_{-1}$ and $VOLH_{-2}$), using the ligand L in which one imidazole ring of the bis(imidazol-2-yl) residue was replaced by a hydrogen atom [L = *N*-glycyl-(imidazol-2-yl)methylamine, Gly-IMA]. Minima were verified through frequency calculations.

Minimisations of the structures formed by Gly-BIMA with the second imidazole ring coordinated in the axial position of the $V^{IV}O$ ion were unsuccessful.

Supporting Information (see also the footnote on the first page of this article): Details of DFT calculations. Comparison between the experimental and calculated $A_{\parallel}$ values for $V^{IV}O$ complexes containing a V–N^{-}(amide) bond, characterised by different and same total equatorial charge (Table S1).

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[43] For example, in the couple **III** of Table S1 $A_{\parallel}$ calcd. for [VO(bpb)] [equatorial donor set (N_{pyr}, N^-, N^-, N_{pyr}) and total equatorial charge –2] has been obtained from $A_{\parallel}$ exptl. of [VO(hypyb)] [156.1×10^{-4} cm^{-1} [21e]], equatorial donor set (N_{pyr}, N^-, N^-, O_{ar}^-) and total equatorial charge –3] with this formula: $A_{\parallel}$ calcd.([VO(bpb)]) = {$A_{\parallel}$ exptl.([VO(hypyb)]) – $A_{\parallel}(O^-_{ar})$ + $A_{\parallel}(N_{pyr})$} = {156.1×10^{-4} cm^{-1} – 38.9×10^{-4} cm^{-1} + 40.7×10^{-4} cm^{-1}} = 157.9×10^{-4} cm^{-1}. Subsequently, $A_{\parallel}$ calcd. (157.9×10^{-4} cm^{-1}) has been compared with $A_{\parallel}$ exptl. (145×10^{-4} cm^{-1}).[21b,21i] The reduction is 8.9%.
[44] For example, Chasteen calculated the contribution to $A_{\parallel}$ for NH_2 and O_{ar}^- from the experimental $A_{\parallel}$ value of $[VO(en)_2]^{2+}$ and $[VO(cat)_2]^{2-}$ complexes, where en = ethylenediamine and cat = catecholate, and for H_2O from experimental $A_{\parallel}$ of aqua ion $[VO(H_2O)_5]^{2+}$[26].
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