Binding of L-Histidine to Vanadium. Structure of *exo*-[VO_2{*N*-(2-oxidonaphthal)-His}]

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The V^{IV} complexes $VO(H_2O)L$ (**2**) (H_2L is a Schiff base derived from *o*-hydroxynaphthalenecarbaldehyde and the amino acids glycine or phenylalanine) react with amines under aerobic conditions to V^V complexes of the general composition VO(OH)L(amine) (**5**) (amine = imidazole, methylimidazole, pyrrole, pyridine, histidine, and histidine derivatives). With alcohols, the complexes VO(OR)L(ROH) (**6**) are formed. Histidine can also replace glycine in **2**, forming the title compound **3** with the histidine moiety coordinating through one of the carboxylate-*O* moieties. Crystallographic data for **3**: $[VO_2\{O_2CCH(CH_2C_3H_4N_2)N{=}CHC_{10}H_6O\}]$, space group *C*2; $Z = 4$, $a = 13.7077(17)$ Å, $b = 6.7390(6)$ Å; $c = 17.1851(15)$ Å, $\beta = 95.644(8)°$, $V = 1579.8(3)$ Å^3, $R = 0.0325$, $R_w = 0.0358$, 3011 reflections (2916 with $I > 2\sigma(I)$). The geometry around vanadium is square pyramidal. The two nitrogens of the imidazole unit are linked by intermolecular hydrogen bonds to the carboxylate oxygens and to the oxo group in the tetragonal plane. **3** models several of the active site features for vanadate-dependent haloperoxidases from marine brown algae.

Introduction

Although vanadium plays an increasingly recognized role as a biometal,[1-4] little is still known of the structure and function of vanadium compounds in living organisms. For one of the two vanadium-dependent enzymes which have been described to date, a haloperoxidase from the marine brown alga *Ascophyllum nodosum*, EXAFS studies suggest a coordination environment for the active V^V site consisting of a doubly bonded oxygen [d(V=O) = 1.61 Å], short (1.72 Å) V—O bonds, and long (2.11 Å) V—O and/or V—N bonds with N possibly stemming from histidine.[5] ESEEM spectroscopy on the reduced (V^{IV}) enzyme has been used to support this view.[6] V–N(His) bonding has also been inferred for, inter alia, V^V and V^{IV} in vanadatransferrin,[7] VO^{2+}–xylose isomerase,[8] the complexes formed between vanadate(V) and ribonucleases,[9] and VO^{2+}–carboxypeptidase.[10] The design of model compounds, preferably with His as a ligand, is therefore of some interest.

The only study on V^V–His interaction available to date is a preliminary report on the complexation of histidine by vanadate in aqueous solution.[11] In three recent reports,[12,13] *N*-coordination of imidazole derivatives to V^V in non-aqueous media has been established. We present here the crystal and molecular structures of a V^V complex, viz. VO_2L' (L'H is the Schiff base formed between 2-hydroxynaphthaldehyde and histidine), where imidazole is not directly involved in coordination to vanadium. The compound displays some of the features revealed by EXAFS for the *A. nodosum* enzyme. Several related complexes are also presented and discussed.

Experimental Section

Materials. The following compounds were obtained from commercial sources: glycine (H_3N^+Gly-O^-), L-phenylalanine (H_3N^+Phe-O^-), L-histidine (H_3N^+His-O^-), *tert*-butoxycarbonyl chloride (BOC-Cl); Sigma and Serva; 2-hydroxynaphthalene-1-carbaldehyde, imidazole and methylimidazole, pyrrole, vanadyl sulfate pentahydrate, Merck; sodium orthovanadate, Janssen. The amines were kept over 4-Å molecular sieves. Published procedures[14] were employed to prepare the *N*-protected (BOC) and *O*-protected (esters) derivatives of H_3N^+His-O^-. In the case of the esters, care was taken to remove all residual HCl. For preparations in water-free systems, solvents were purified by drying and subsequent distillation under nitrogen.

Spectra. ^{51}V NMR spectra were obtained on a Bruker AM 360 spectrometer at 94.73 MHz in 10 mm diameter rotating vials. Typical measuring parameters: sweep width, 125 KHz; time domain, 8 K; pulse angle, 60°; line broadening factor, 30 Hz; no relaxation delay. All $\delta(^{51}V)$ values are quoted relative to $VOCl_3$ as external standard.

EPR spectra were recorded on a Bruker ECS 106 spectrometer (equipped with a Bruker microwave bridge ECS 041 MR) at 9.78 GHz at a microwave power of 5 mW. IR spectra were obtained on a Perkin-Elmer 1720 FT spectrometer as Nujol mulls (CaF_2 plates) or in KBr.

X-ray Crystallography. Data were collected on a Syntex $P2_1$ diffractometer at room temperature in the $\theta/2\theta$ scan mode using a graphite monochromator and Mo Kα radiation. The structure was solved by the use of the program system SHELXS-86 and refined with SHELX-76. Absorption corrections have not been carried out. Non-hydrogen atoms were refined anisotropically. All hydrogen atoms except of the H in the vicinity of the imino N (N16, cf. Figure 1) were obtained from a Fourier difference synthesis and refined isotropically. The H on N16 was not explicitly considered in the refinement (see Results and Discussion for further details). For additional information on the solution and refinement of the structure see Table I.

Preparation of Complexes. [$VO(H_2O)$\{N-(2-oxidonaphthal)-Gly-O^-\}] (2a) and [$VO(H_2O)$\{N-(2-oxidonaphthal)-Phe-O^-\}] (2b) (cf. Chart I). The syntheses of these compounds follow published procedures for the preparation of amino acid based Schiff base ligands[15] and corresponding salicylidene complexes of V^{IV}.[16] Solvents (water and ethanol) were

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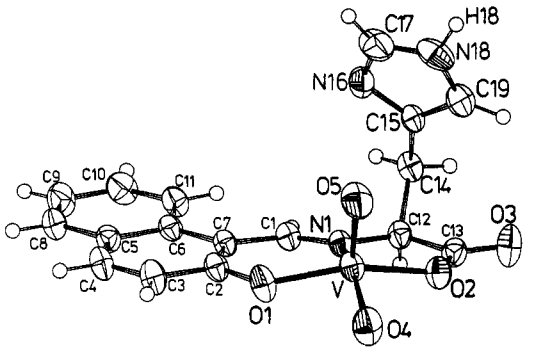
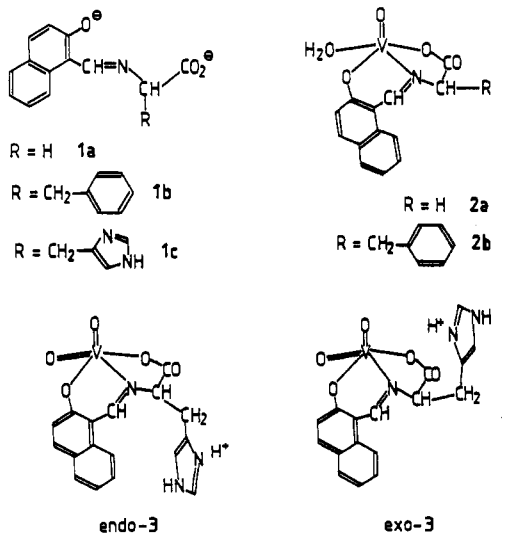


Figure 1. ORTEP diagram of **3**, showing 50% probability ellipsoids. The proton in the vicinity of N16, which was not found from the Fourier difference map, is not shown.

Table I. Structure Solution and Refinement for **3**

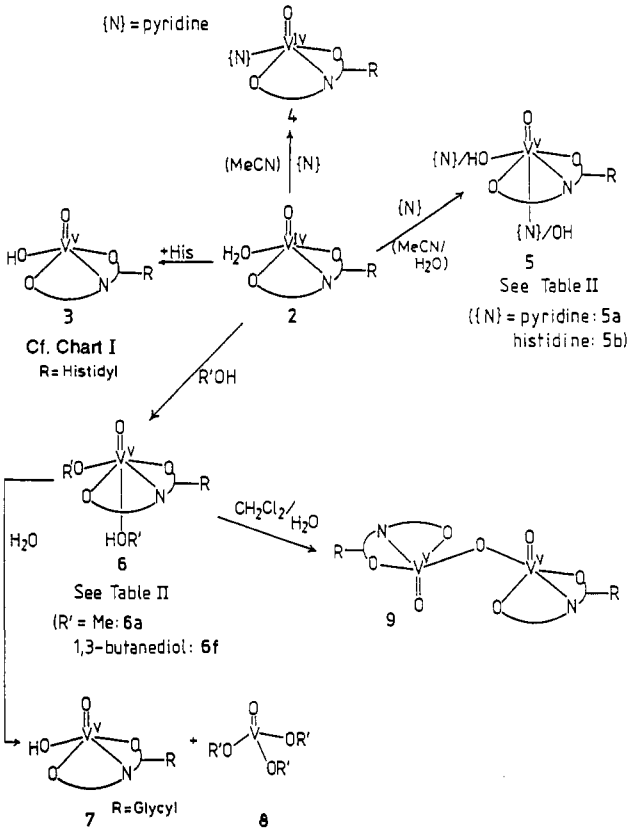
cryst dimens, mm	0.3 × 0.3 × 0.4
empirical formula	$C_{17}H_{14}N_3O_5V$
molar mass, g mol^{-1}	391.26
space group	*C*2
cell params	
a, Å	13.7077(17)
b, Å	6.7390(6)
c, Å	17.1851(15)
β, deg	95.644(8)
no. of formula units	4
cell volume, Å^3	1579.8(3)
calcd density, g cm^{-3}	1.645
linear abs coeff, cm^{-1}	7
no. of obsd reflcns	3011
no. of significant reflcns ($\|F_o\| > 4\sigma(F_o)$)	2916
scan range, deg	$4.5 < 2\theta < 45.0$
no. of refined params	248
hkl region	h, 0 → 20; k, 0 → 10; l, −21 → +21
check reflexes	6,6,8; 3,3,15; 12,2,4
F(000)	672
difference Fourier synthesis	
max, e Å^3	0.513
min, e Å^3	−0.364
R value ($\Sigma\|F_o - F_c\|/\Sigma\|F_o\|$)	0.0325
R_w value ($\Sigma w(\|F_o - F_c\|)^2/\Sigma w\|F_o\|^2$)	0.0358

Chart I



degassed and saturated with N_2, and the preparation was carried out under N_2: 0.050 mol of the amino acid (3.75 g $H_3N^+Gly\text{-}O^-$ or 8.26 g $H_3N^+Phe\text{-}O^-$, respectively) and 13.61 g (0.10 mol) of sodium acetate trihydrate were dissolved in 100 mL of water. This solution was treated with 8.61 g (0.050 mol) of 2-hydroxynaphthalene-1-carbaldehyde dissolved in 125 mL of ethanol. To these solutions was added portionwise and with

Scheme I



stirring 10.8 g (0.0427 mol) of $VOSO_4 \cdot 5H_2O$ in 40 mL of water. The green precipitates of **2a** and **2b**, containing the Schiff base ligands **1a** and **1b** (Chart I), were filtered off after 30 min of stirring, washed three times with 30-mL portions of water/ethanol 1/1 and finally with ether, and dried under vacuum. The compounds **2a** and **2b** are slightly soluble in dmf and CH_3CN and are insoluble in water, acetone, and ether. **2a**: yield 10.5 g (79% related to $VOSO_4 \cdot 5H_2O$). Anal. Calcd for $C_{13}H_{11}NO_5V$: C, 50.00; H, 3.52; N, 4.49; V, 16.33. Found: C, 50.02; H, 3.73; N, 4.61; V, 16.32. IR (KBr, cm^{-1}): ν(V=O) 980. EPR (2 mmol of CH_3CN, room temperature): g_{iso} 1.975; A_{iso} (Hz) 102. **2b**: yield 12.8 g (74%). Anal. Calcd for $C_{20}H_{17}NO_5V$: C, 59.71; H, 4.26; N, 3.49; V, 12.66. Found: C, 59.62; H, 4.49; N, 3.82; V, 12.94. IR (KBr, cm^{-1}): ν(V=O) 998. EPR (2 mmol in CH_3CN, room temperature): g_{iso} 1.976; A_{iso} (Hz) 102.

In an extra preparation without $VOSO_4$, the ligand **1a** was also isolated after a 40 h reaction time in 85% yield, and its purity confirmed by elemental analysis.

[VO_2{N-(2-oxidonaphthal)-(H^+)His-O^-}] (3). A 75-mg (0.24-mmol) sample of compound **2a** was dissolved/suspended in 15 mL of CH_3CN and treated with 5mL of an aqueous solution containing 150 mg (0.967 mmol) of histidine. The mixture was stirred overnight under aerobic conditions to yield a yellow brown solution from which, when kept at ca. 5 °C, yellow crystals of *exo*-**3** (Scheme I), suitable for an X-ray analysis, separated in the course of several days. From the mother liquor, additional product was isolated. Yield: 640 mg (68 %). ^{51}V NMR (CD_3CN/H_2O; δ, ppm (relative integral intensity)): −546 (**8**), *exo*-**3**; −560 (1), *endo*-**3**. IR (Nujol, cm^{-1}): (OH/NH) 3300–3152 (broad band), 3132, ν(C=N) 1623, $\nu_{as}(CO_2^-)$ 1609, ν(V=O) 941. Crystals of *exo*-**3**, when redissolved in CH_3CN, provided the $\delta(^{51}V)$ signals for both, *exo*- and *endo*-**3**.

Reaction between 2, Cyclic N-Bases, and Alcohols (cf. Scheme I). [VO(Me-im){N-(2-oxidonaphthal)-Gly-O$^-$}] (4) precipitated as a light green powder from a solution containing 0.80 g (2.56 mmol) of **2a** and 1.26 g (1.3 mL, 15.3 mmol) of methylimidazole in 10 mL of absolute MeCN stirred under anaerobic conditions. **4** was filtered off and dried under

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Table II. ^{51}V NMR Data for the Complexes **5** and **6** (Cf. Scheme I)

complex (ligand)	R	$\delta(^{51}V)^a$	other
5a (pyridine)	H	−540	
5b (histidine)	H	−541	
	CH_2Ph	−542	
5c (H_2N-His-OMe)	H	−538	
5d (BOC-His-OH)	H	−540	
5e (imidazole)	H	−539	
5f (methylimidazole)	H	−538	
5g (pyrrole)	H	−534	
6a[b] (methanol)	CH_2Ph	−556(1), −564(3)	−547(0.3) [$VO(OMe)_3$]
6b (ethanol)	CH_2Ph	−563(1), −569(3)	−598(0.2) [$VO(OEt)_3$]
6c, (3,3′-dimethyl-2-butanol)	CH_2Ph	−574(1),[c] −579 sh/ −582(0.7)	−621/−622(0.3) [$VO(OR')_3$]
6d (*tert*-butyl alcohol)	CH_2Ph	−590	
6e (1,2-propanediol)	CH_2Ph	−540[d]	
6f[e] (1,3-butanediol)	CH_2Ph	−571[c] and −574(1.4); −585[d] and −587(1)	−610, −623 (<0.05)
6g (2-methyl-2,4-pentanediol)	CH_2Ph	−581[c] and −585/ −587[f] (1)	−598(0.6) [$VO(OR')_3$]

[a] In CD_3CN, except were indicated otherwise. Where more than one signal is observed, relative intensities are given in parentheses. The less intense signal is assigned the (sterically less favorable) endo, the more intense the exo isomer of the complex. [b] In CD_3OD. [c] With a shoulder at low field. [d] Only one signal is observed in this case, probably due to chelate ring formation by $HOCH(Me)CH_2O^-$, an assumption supported by the relatively low ^{51}V shielding for a 5-membered ring.[22] [e] See Figure 3. [f] Only partly resolved.

vacuum. Yield: 0.4 g (42% related to **2a**). Anal. Calcd for $C_{17}H_{15}N_3O_4V$: C, 54.27; H, 4.02; N, 11.17. Found: C, 54.32; H, 4.15; N, 11.22. IR (Nujol, cm^{-1}): ν(C=N) 1622, $\nu_{as}(CO_2^-)$ 1607, $\nu_s(CO_2^-)$ 1393, ν(O—Ph) 1305, ν(V=O) 990. The brown filtrate contained a V^V compound (^{51}V NMR evidence; $\delta(^{51}V) = -532$ ppm), which was not further identified.

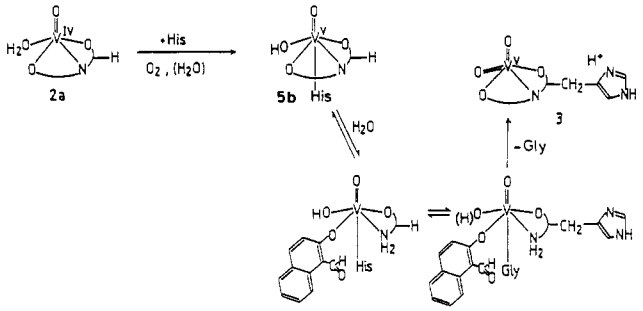
[VO(OH)(pyridine){N-(2-oxidonaphthal)-Phe-O$^-$}] (5a) was obtained as an orange powder from the reaction of 0.27 g (0.67 mmol) of **2b** in 4.0 mL of pyridine and 2 mL of H_2O at 75 °C. Anal. Calcd for $C_{25}H_{21}N_2O_5V$: C, 62.21.; H, 4.21; N, 5.84. Found: C, 62.26; H, 4.61; N, 6.1. ^{51}V NMR (CD_3CN; δ, ppm): −540. IR (Nujol and KBr, cm^{-1}): (OH) 3334–3438 (broad), ν(C=N) 1622, $\nu_{as}(CO_2^-)$ 1609, $\nu_s(CO_2^-)$ 1393, ν(O—Ph) 1308, ν(V=O) 994. All other complexes belonging to category **5** were prepared from **2a** or **2b** at room temperature in 15 mL of CH_3CN containing 2 mL of water, with a 4-fold molar excess of the amine, and were characterized by ^{51}V NMR in solution (Table II).

[VO(OMe)(HOMe){N-(2-oxidonaphthal)-Phe-O$^-$}] (6a). In a reaction typical for the preparation of the category **6** complexes, 1.0 g (2.5 mmol) of **2b** was dissolved in 16 mL of absolute methanol to give a reddish brown solution. After ca. 1 h of stirring, the solvent was slowly evaporated to dryness under high vacuum. Yield: 0.7 g (63%) of **6a**. Anal. Calcd for $C_{22}H_{21}NO_6V$: C, 59.20; H, 4.70; N, 3.14; V, 11.43. Found: C, 58.8; H, 5.0; N, 3.4; V, 11.0. ^{51}V NMR (CD_3CN; δ, ppm): −556, −564 (*endo*- and *exo*-**6**). IR (KBr, cm^{-1}): ν(OH) 3279 (broad), ν(C=N) and $\nu_{as}(CO_2^-)$ centered at 1622 (broad), $\nu_s(CO_2^-)$ 1394, ν(O—Ph) 1305, ν(V=O) 978. $VO(OMe)_3$ was formed as a by-product. All other type **6** complexes (cf. Table II) were prepared accordingly. Reaction times are longer (up to 2 days) for secondary and tertiary alcohols.

Results and Discussion

Characterization of the Naphthal Complexes 2 and 3. Various vanadium compounds containing the $VO(O_xN_y)$ unit ($x + y$ = 4–6) have been described during the last few years,[17-21] among these complexes with amino acids[18] and amino acid derivatives[17] (mostly amino acid Schiff bases of salicyl aldehyde) and complexes which may be considered to mimic histidine binding because they contain imidazole derivatives,[12,13] pyrazolyl,[20a] or a pyridine *N*.[20b,c] Structural data are scarce, however, and restricted, in the case of complexes containing amino acid derivatives, to the salicylidene complexes [VO(OMe)(MeOH)sal-ala][17c] and [{VO(sal-aa)}$_2\mu$-O] (aa = alanate[17c] and serinate).[17f]

The formation of Schiff bases from amino acids and aromatic aldehydes usually is a slow process. VO^{2+} ions, however, enable an accelerated template synthesis. Thus, when 2-hydroxynaphthalene-1-carbaldehyde and glycine or phenylalanine are reacted in the presence of vanadyl sulfate and under an inert gas atmosphere, immediate condensation to the Schiff base, deprotonation of the phenolic hydroxy group and coordination to the vanadyl cation occur (complexes **2a** and **2b**). H_2-**1a** (the ligand system of **2a**; cf. Chart I), when treated with histidine in H_2O/EtOH, undergoes partial reorganization to H_2-**1c**. If **2a** is stirred with histidine under aerobic conditions, this reorganization takes place at the vanadium center, and the equilibrium shifts toward a practically complete conversion of **1a** to **1c** and hence formation of the V^V complexes **3**, in which the water ligand of the V^{IV} complex **2a** is deprotonated to an oxo ligand in the course of the oxidation of V^{IV} to V^V by oxygen. There is evidence from ^{51}V NMR data (see the following section) that, prior to the reorganization of the ligand system, histidine is coordinated to vanadium through the tertiary amino group, forming the intermediate **5b** (eq 1).



(1)

Compound **3** has two centers of chirality (vanadium and C_α of the amino acid moiety) and hence should exist as two diastereomers, corresponding to an exo and an endo form. Only *exo*-**3** crystallizes from the solution (monoclinic space group C2). Figure 1 shows an ORTEP view of the complex; Figure 2 represents the intermolecular contacts through hydrogen bridges. Data from the crystal structure determination are contained in Table I (vide supra), selected bond lengths, bond angles, and best planes in Table III, and fractional coordinates together with isotropic thermal factors in Table IV. Vanadium is in a tetragonal-pyramidal environment, with the doubly bonded oxygen O5 in

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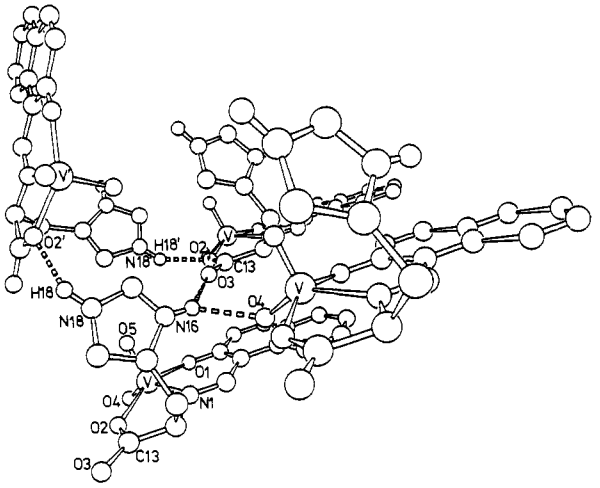

Figure 2. Illustration (SCHAKAL representation) of the intermolecular hydrogen bonding interactions (broken lines).

Table III. Selected Bond Distances (Å), Angles (deg), and Best Planes (deviations in Å) for **3**

Bond Distances			
V–O1	1.890(2)	N1–C12	1.475(3)
V–O2	2.006(2)	C12–C13	1.522(4)
V–O4	1.649(2)	C12–C14	1.533(3)
V–O5	1.604(2)	C14–C15	1.489(3)
V–N1	2.163(2)	N16–C15	1.368(4)
O1–C2	1.308(3)	N16–C17	1.344(4)
N1–C1	1.292(3)	N18–C17	1.309(5)
C2–C7	1.397(3)	N18–C19	1.361(4)
O2–C13	1.290(3)	C15–C19	1.363(4)
O3–C13	1.208(3)	N18–H18	0.89(3)
O2···H18′	1.98(4)		

Bond Angles			
O1–V–N1	82.54(8)	V–N1–C1	127.4(2)
O1–V–O2	149.46(8)	V–O1–C2	136.6(2)
O1–V–O4	96.5(1)	V–N1–C12	116.2(2)
O2–V–N1	74.83(9)	N1–C1–C7	126.1(2)
O2–V–O4	88.9(1)	O1–C2–C7	124.2(2)
O4–V–N1	141.1(1)	C1–C7–C2	119.7(2)
O5–V–O1	106.4(1)	O2–C13–O3	122.7(3)
O5–V–O2	100.1(1)	O3–C13–C12	115.8(2)
O5–V–O4	109.2(1)	N1–C12–C13	107.4(2)
O5–V–N1	108.2(1)	C12–C14–C15	112.9(2)

LSQ Planes	
plane 1a	O1(–0.082)–O2(–0.089)–O4(0.085)–N1(0.085)
plane 1b	O1(–0.009)–O2(–0.009)–N1(0.071)–C1(0.033)–C13(0.027)–O3(0.016)
plane 2	O1(0.018)–O2(–0.004)–O3(–0.002)–N1(–0.071)–C1(0.030)–C2(–0.002)–C7(–0.003)–C12(0.017)–C13(0.018)
plane 3	N16(–0.007)–N18(–0.004)–C15(0.004)–C17(0.007)–C19(0.001)

the apex. The histidine part of the ligand system evades coordination through an imidazole N. Rather, one of the oxygens (O2) of the carboxylate function coordinates as a part of the tetragonal plane (plane 1a), possibly as a consequence of the high oxophilicity of V^V and involvement of N16 in intermolecular H bonds discussed in detail below. The tetragonal plane is further spanned by a second oxo group (O4), the phenolate oxygen O1, and the nitrogen N1 of the Schiff base link. Vanadium extends from this plane by 0.41 Å. The complete ligand system stretching from O1 to C12, C13, and O2/O3 (the carboxylate oxygens) is essentially planar (plane 2). From C12 extends, in an exo position, the methylene–imidazole substituent. The imidazole ring itself again is planar (plane 3) and kinked toward the V=O axis and plane 1b. The angle between planes 1b and 3 amounts to 65.3°. There are intermolecular contacts between the coordinated carboxylate oxygen O2 and (NH)18′ from the imidazole group of a symmetry-related molecule in the adjacent unit cell, (Figure 2; d(O2–N18′) = 2.786(3), d(O2–H18′) = 1.98(4) Å), giving rise to the crystallographic C_2 axis.

Table IV. Fractional Coordinates and Isotropic Temperature Factors of the Non-Hydrogen Atoms and H18 of **3**

atom	x/a	y/b	z/c	U_{eq}, Å^2
V	0.11641(2)	0.00000(0)	0.80443(2)	0.0320(3)
N1	0.25683(11)	0.0166(4)	0.75729(8)	0.0281(12)
O1	0.08502(10)	0.2060(3)	0.73009(9)	0.0423(15)
O2	0.18066(11)	–0.2578(3)	0.83254(9)	0.0392(13)
O3	0.31297(14)	–0.4386(3)	0.85723(12)	0.056(2)
O4	0.01021(12)	–0.1111(4)	0.79211(11)	0.053(2)
O5	0.1270(2)	0.1094(4)	0.88813(9)	0.056(2)
C1	0.28727(14)	0.1507(4)	0.71183(11)	0.030(2)
C2	0.13324(14)	0.3359(4)	0.69204(10)	0.031(2)
C3	0.07794(14)	0.4982(5)	0.65735(11)	0.040(2)
C4	0.1203(2)	0.6383(4)	0.61479(12)	0.039(2)
C5	0.2215(2)	0.6279(4)	0.60274(10)	0.032(2)
C6	0.27855(13)	0.4684(4)	0.63615(10)	0.029(2)
C7	0.23261(14)	0.3196(4)	0.68103(10)	0.0281(14)
C8	0.2649(2)	0.7751(4)	0.55920(13)	0.041(2)
C9	0.3630(2)	0.7651(5)	0.54800(14)	0.050(2)
C10	0.4197(2)	0.6114(5)	0.58196(13)	0.046(2)
C11	0.38001(14)	0.4669(4)	0.62477(12)	0.038(2)
C12	0.3260(2)	–0.1452(4)	0.78042(11)	0.031(2)
C13	0.2717(2)	–0.2956(4)	0.82653(11)	0.035(2)
C14	0.41906(14)	–0.0780(4)	0.83108(11)	0.033(2)
C15	0.39731(12)	0.0166(4)	0.90574(10)	0.0297(14)
N16	0.3929(2)	0.2178(4)	0.91428(12)	0.044(2)
C17	0.3690(2)	0.2611(5)	0.9856(2)	0.059(3)
N18	0.3603(2)	0.0961(5)	1.02277(11)	0.050(2)
H18	0.362(2)	0.102(5)	1.077(2)	0.053(2)
C19	0.3765(2)	–0.0613(5)	0.97533(13)	0.041(2)

The vanadium-to-ligand bond lengths fall well within or are close to the range usually observed with related compounds. Thus, d(V–O1) = 1.890(2) Å compares with V–O(phenolic) bond distances of 1.83–1.90 Å in salen,[17c,23a] phenol,[20a] and oxine[23b] complexes. Similarily, d(V–N1) = 2.164(2) Å in **3** may be compared with d(V–N) of 2.08–2.17 Å in other Schiff base complexes.[17c,23a,24] The V–O(carboxylate) distance of 2.007(2) Å in **3** is longer than the usual range of 1.92–1.99 Å reported for monodentate vanadium carboxylates.[17c,f] V=O bond lengths in vanadium compounds containing the VO or *cis*-VO_2 center commonly range from 1.56 to 1.61 Å, clustering around 1.57 Å. d(V–O5) = 1.604 Å is within this range. d(VO) = 1.647 Å has been reported for the complex [{$Q_2VO_2Na(H_2O)_2$}$_2$(μ-dmf)] (Q = 8-oxyquinolate(1–)), containing a VO···Na grouping.[25] An elongated bond, viz. d(V–O4) = 1.649 Å, is also observed for **3**. Although there is a band in the IR spectrum at 657 cm^{-1}, coinciding with the ν(V–OH) reported for [{LVO(OH)}$_2$(μ-O)] (L = triazacyclononane),[26] the bond in **3** is too short for a V–OH group, and **3** is formulated as a dioxo species for this reason.

V–OH bonds for nonbridging hydroxides have sporadically been noted in oxovanadium clusters. In a typical example, $H_2V_{10}O_{28}^{4-}$, the mean V–O distances involving the protonated oxygens are 1.944 Å.[27] Information on molecular vanadium complexes with a hydroxide ligand are even more scarce. For the dimeric V^{IV} complex [{LVO(OH)}$_2$(μ-O)]$^{2+}$, d(V–OH) = 1.783 Å has been reported.[25] The question then arises as to where the lacking H^+ in **3** resides. We have not been able to locate this hydrogen from a difference Fourier map (for all the other hydrogens in the molecule this has been achieved). We have therefore resorted to intermolecular contacts and to valence bond

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Table V. Experimental Bond Lengths d (Å) and (Sum of) Bond Numbers s

atom	bond lengths (d)	s
O1	O1–V (1.890), O1–C2 (1.308)	1.99
O2	O2–V (2.006), O2–C13 (1.290), O2–H18 (1.98)	2.03
O3	O3–C13 (1.208)	1.74
O4	O4–V (1.649)	1.52
N16	N16–C15 (1.369), N16–C17 (1.344)	2.70
N18	N18–C17 (1.309), N18–C19 (1.360), N18–H18 (0.896)	3.73

numbers. There are intermolecular contacts between the imino-*N* of imidazole (N16) and O3, the uncoordinated carboxylate-*O* (d = 2.699 Å), and also between N16 and the oxo ligand O4 (d = 2.980 Å). This is in the range documented for *N*(amine)···H···O interaction[28] and hence suggests an H-bond network between N16, O3 and O4 (Figure 2) in addition to the hydrogen bond between N18 and O2.

The valence bond numbers $s = (d/R_o)^{-N}$ developed by Brown[29] have successfully been used to detect oxygen protonation sites in, inter alia, oxovanadium clusters.[30] d is the experimental bond distance, R_o and N are listed[29] constants typical of an atom A bonded to an atom B. Ideally, s = 2 for oxygen, and 3 or 4 for nitrogen. Table V summarizes the s values for the imidazole nitrogens and equatorial oxygens present in compound **3**. Considering the oxygens, O4 and, to a lesser extent, also O3 are unsaturated with respect to the valence bond order. The distances between the "obscured" H and the three atoms under consideration, obtained from the differences between calculated and ideal s values, amount to d(N16–H) = 0.77 Å, d(O4···H) = 1.23 Å, and d(O3···H) = 1.61 Å, providing evidence for the protonation of N16. Similar interatomic bond lengths, (and intramolecular bonding parameters for the imidazole moiety) have been observed in the copper complexes $CuCl_2$(His) and $Cu(His)_2(NO_3)_2$,[31] where histidine is also coordinated through one of the carboxylate oxygens, and a similar H-bond network exists.

Reactions of Compound 2. If water is excluded, **2** reacts with pyridine to form, inter alia, a light green V^{IV} complex, **4**. Similar (but impure; by elemental analyses) complexes have been obtained with other amines. Under aerobic conditions, and preferably with the addition of some water, **2** has a marked tendency to be oxidized in the presence of *N* and *O* bases. The various products formed when **2a** is reacted with cyclic amines on the one hand, and with alcohols on the other hand are summarized in Scheme I. Table II in the Experimental Section contains a collection of ^{51}V NMR chemical shifts. Pyridine yields a yellow-orange compound with a characteristic $\delta(^{51}V)$ of –540 ppm, tentatively formulated as a pyridine adduct (**5a**) of oxidized **2** on the basis of spectroscopic evidence and the elemental analysis, following a previous suggestion for the corresponding salicylidene complex of V^{IV}.[17a] The same signal positions allocated to type **5** complexes have been observed for imidazole (im), methylimidazole (Me-im), H_3N^+His-O^- (compare also eq 1), H_2N-His-OMe and BOC-His-OH. Me-im has available tertiary amine-*N* only. Since im and Me-im give rise to almost the same $\delta(^{51}V)$ values, coordination is probably through the tertiary N in both cases, and this is also assumed for histidine. Coordination via the amino or carboxylate functions can be excluded, since the N- and O-protected forms of histidine also give rise to a signal at or close to –540 ppm. Pyrrole, with a secondary amine-*N* only, produces a signal at –534 ppm. For the complexes formed between **2b** and im or Me-im, there is, along with the main resonance around –538 ppm (possibly the sterically more favorable *exo* form of **5**), a second, less intense signal shifted upfield by 9 ppm. This may account for the formation of some *endo*-**5** under these conditions. We have shown earlier, for the complexes $VO(oxine)_2$(alkoxide), that a difference of ca. 10 ppm for the ^{51}V chemical shifts of diastereomers is what one can expect for a two-bond separation of chiral centers.[32] The extent of $\Delta\delta$ for diastereomers is governed by the overall steric situation and hence may vary.

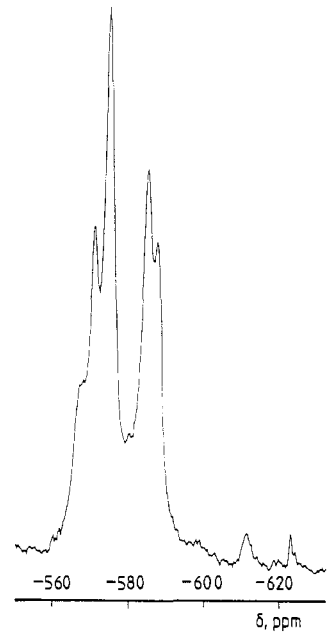

Figure 3. ^{51}V NMR spectrum of **6f**, the compound formed from **2b** and 1,3-butanediol. The multiplicity of the signal reflects the various diastereomers present in solution for this compound with four centers of chirality (*V*, *C* of the Phe moiety, secondary *C*s of R′OH and R′O$^-$). The two low-intensity signals at high field probably correspond to vanadate esters **8**.

2 reacts with excess alcohol to the six-coordinated V^V complexes **6**. A compound closely related to the type **6** complexes, viz. VO(OMe)(HOMe)(salicylidene-Gly-O$^-$) has originally been described by Fraûsto da Silva[17a] and recently been structurally characterized by Nakajima et al.[17c] The salicylidene complex is in the exo configuration. The ^{51}V chemical shifts (Table II) are upfield of the amine complexes **5**, as expected for V^V with the more electronegative (less polarizable) *O* donor ligands[22,32] ("*inverse* electronegativity dependence of metal shielding"[33]). In all cases where **2** is reacted with alcohols, two ^{51}V resonances are observed and assigned the endo and exo form of **6**, with the latter belonging to the more intense signal at higher field. The separation of the two signals amounts to ca. 8 ppm. Shielding of the ^{51}V nucleus increases in the sequence primary < secondary < tertiary alcohol. The same increase of shielding has been noted for $VO(oxine)_2(OR')$[32a] and $VO(OR')_3$[33,34] and explained alternatively by a steric effect[33] or an electronic effect,[35] namely an increase of the V–OR′ bond strength in the same sequence by an increase of the fractional negative charge at oxygen. If an additional center of chirality is introduced, as with 3,3-dimethyl-2-butanol or 1,3-butanediol, the signal pattern becomes even more complex (Figure 3). Hydrolysis of **6** yields **7** (i.e. the oxidized form of **2**, or the glycine equivalent of **3**) and the vanadate esters

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8 as decomposition product. No further hydrolytic degradation[36] was observed under the conditions maintained in our experiments. In several cases, vanadate esters were also generated as byproducts in the formation of **6** (Table II). If hydrolysis of **6** is carried out in wet CH_2Cl_2, the known blue, dinuclear V^V complex **9**[17c] is obtained.

Conclusion

Under aerobic conditions H_3N^+His-O^- coordinates to preformed, pentavalent Schiff base complexes such as [VO(H_2O)(Y-Gly-O^-)] **2a** (Y derives from 2-hydroxynaphthalene-1-carbaldehyde) through the tertiary imidazole-*N*, as do N- and O-protected His, imidazoles, pyrrole, and pyridine, probably increasing the coordination number to **6**. Simultaneously, V^{IV} is oxidized to V^V. But histidine is also able, in the presence of oxygen and water, to replace glycine in **2a**, forming the complex [VO_2{Y(H^+)His-O^-}] (**3**). The histidine moiety in **3** coordinates through the carboxylate oxygen. There is also H-bond interaction between this oxygen and the imidazole-*NH* of a symmetry-related molecule, and between the (protonated) imino-*N* of imidazole and the oxygens O3 and O4 of adjacent molecules. This is of significance for, inter alia, the hydrogen bonding network in vanadate–enzyme complexes such as vanadate–ribonuclease-T_1.[37] The presence of hydrogen bridges leads to elongations of the bonds of vanadium to those oxygens which are involved in the H-bond network beyond what is observed in related complexes lacking such an interaction.

3 fulfills some of the active site patterns noted for vanadate-dependent haloperoxidases from the seaweed *A. nodosum*. Thus, EPR studies of the reduced (V^{IV}) holoenzyme[38] have revealed at least one protonation/deprotonation site, provided, in our model, by the coordinated carboxylate function and its H-link to N18 of imidazole, and by the proton ambiguity between N16, O3 and O4.[39] These interesting features have consequences also for judging the bond lengths for the native (V^V) and the reduced enzyme, obtained from EXAFS studies:[5] Our results indicate that a bond length of 1.72 Å in the enzyme does not necessarily result from a vanadate ester bond (formed by, e.g. serine), but may also be traced back to an unusual elongation of a vanadyl oxygen by H-bond interaction. Nor does a long vanadium-to-ligand bond (2.11 Å) necessarily indicate a nitrogen donor but may also result from a (partially) protonated carboxylate.

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Supplementary Material Available: Listings of atomic coordinates and anisotropic temperature factors of all atoms, and bond lengths and bond angles (4 pages). Ordering information is given on any current masthead page.

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