[VO{*N*-(2-oxido-1-naphthylmethylene)-L-ala}OBu^s(HOBu^s)]: Characterization of a Complex containing Four Centres of Chirality

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Reaction of vanadyl sulfate, L-alanine and 2-hydroxynaphthaldehyde with subsequent aeration in D,L-*sec*-butyl alcohol leads to the Schiff base V^V complex [VO{*N*-(2-oxido-1-naphthylmethylene)-L-ala}OBu^s(HOBu^s)] which, in solution, exists in at least three diastereoisomers (^{51}V NMR evidence), and crystallizes with the *ASRR* and *CSSS* isomers in the same asymmetric unit.

Oxovanadium(v) complexes containing a mixed *ON* coordination sphere (including an enamine *N*, a carboxylate *O* and an alkoxide *O*) are considered model compounds for the active centre in vanadate-dependent bromoperoxidases (V-BrOP) from seaweeds.[1] V^V, mainly in the form of vanadate $H_2VO_4^-$, also attains a more general physiological role as an inhibitory or stimulating agent for phosphate metabolizing enzymes,[2a] including the activation of tyrosine kinase and/or inhibition of tyrosine phosphatase, which are involved in triggering the insulin receptor mechanisms for intracellular insulin intake.[2b] On this general background, it is of interest to investigate the binding of V^V (and also of V^{IV}, since V^V is easily reduced to V^{IV} in the intracellular medium) to proteins, peptides and amino acids or molecules containing amino acid constituents. While the aqueous systems containing vanadate or vanadyl and an amino acid or small peptide have been studied to a certain extent during the last few years, using methods such as ^{51}V NMR, EPR, potentiometry and UV–VIS spectroscopy,[3,4] crystal structure determinations to verify the proposed structures in solution are not yet available on these systems. On the other hand, a few crystal structure accounts have appeared recently on complexes containing an amino acid as the amine component of a Schiff base, *viz.* [V^{IV}O(sal-ala)H$_2$O] (sal = *N*-salicylidene),[5] [V^{IV}O(sal-gly)(py)$_2$] and [V^{IV}O(sal-ala)bipy],[6] [V^{IV}(sal-ser)(μ-O)V^V(sal-ser)],[7] [V^{V}O(sal-ala)OMe(HOMe)],[8] and [VO$_2$-(naph-his)] (naph = *N*-2-oxido-1-naphthylmethylene).[9] In all of these cases, the amino acid ligates through one of the carboxylate oxygens; side chains (the hydroxy group of serine or the enamine nitrogen of histidine) are not involved in coordination. Where there is a centre of chirality in the ligand system (the Cα of the amino acid component) in addition to the chiral vanadium centre, as in the case of the alanine, serine and histidine complexes, the crystal structures indicate the presence of one diastereomer only.

As described earlier,[9] vanadyl sulfate, L-alanine and 2-hydroxynaphthaldehyde react in acetate buffered, oxygen-free ethanol : water (1 : 1 *v*/*v*) to form the Schiff base complex [V^{IV}O{*N*-(2-oxido-1-naphthylmethylene)-L-ala}H$_2$O], **1**. A solution of **1** in D,L-*sec*-butyl alcohol, on aeration, yielded crystalline [V^{V}O{*N*-(2-oxido-1-naphthylmethylene)-L-ala}OBu^s(HOBu^s)], **2**.

2 crystallizes in the monoclinic space group $P2_1$. There are four centres of chirality, *viz.* the vanadium, the α-carbon of the alanine moiety, and the secondary carbons of the ligated butanol and butanolate. Of the eight possible diastereoisomers [(*A* or *C*)(*S*)(*R* or *S*)(*R* or *S*), where *A* and *C* correspond to the chirality at the vanadium centre], two (*ASRR* and *CSSS*) are represented by two independent molecules in the asymmetric unit. A SCHAKAL plot of the molecules is shown in Fig. 1, selected bonding parameters are contained in the legend to Fig. 1. The molecular structure corresponds to that of a flat tetragonal pyramid with the doubly bonded oxygen at a normal bond length [1.604(9) and 1.584(8) Å] in the apex, and the nitrogen, the phenolate oxygen, one of the carboxylate oxygens and the butanolate oxygen forming the plane. Vanadium deviates from this plane by 0.302 Å. In the *trans* position to the oxo ligand is the butanol, coordinated to the vanadium at a rather long distance of 2.328(8) [2.302(8) Å in the second molecule], thus giving rise to a highly distorted octahedron for the overall geometry. The bond lengths *d*(V-OHR) in **2** are slightly shorter than in [VO(sal-ala)OMe(HOMe)] [2.384(4) Å].[8] Other bonding parameters compare to those of the Schiff base complexes noted above. The hydroxy groups of the butanol ligands of the two molecules of the asymmetric unit are involved in intermolecular hydrogen bonds to the uncoordinated carboxylate oxygens, as shown by the distances O(6)···O(9) = 2.692 and O(3)···O(12) = 2.756 Å.

Complex **2** represents, apart from the V=O group, three structural features which have been derived for V–BrOP from EXAFS studies:[1] A short V–O single bond [to the alkoxide: V(1)–O(5), 1.76; 1.72 Å in V–BrPO], a 'normal' V–O single bond [to the carboxylate: V(1)–O(2), 1.94; 1.91 Å in V–BrOP], and a relatively long V–N distance [V(1)–N(1), 2.10; 2.11 Å in V–BrPO]. In the light of the interaction of V^V with tyrosine kinases and phosphatases, the bonding to the phenolic oxide [V(1)–O(4), 1.86 Å] is also of interest.

The ^{51}V NMR spectrum of a solution of **2** in a mixture of butanol and CD_2Cl_2 [Fig. 2(*a*)] exhibits three signals [plus a fourth one at higher field, which is due to VO(OsBu)$_3$ formed by partial alcoholysis of **2**], while the corresponding salen complex [VO(sal-L-ala)OBu^s(HOBu^s)] shows four signals in the ^{51}V NMR [Fig. 2, (*b*)] to be expected for at least four diastereoisomers. The diastereoisomer splitting, several ppm, is of the same order of magnitude as observed in other multichiral vanadium complexes, where the asymmetric V centre is separated from the centres of chirality in the ligand periphery by two or three bonds.[9,10] There are several reasons for the observation of only three or four signals where eight diastereo-

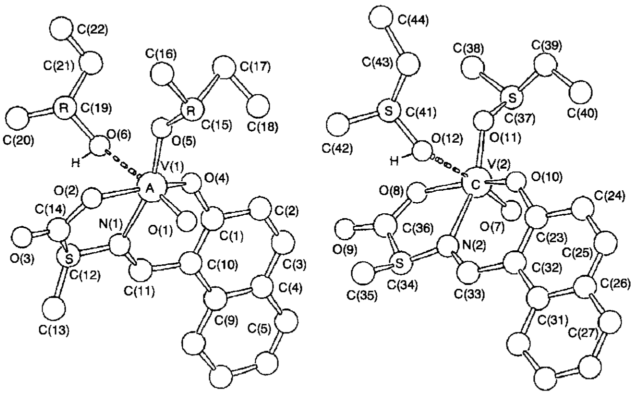

Fig. 1 SCHAKAL plots and numbering schemes of the two independent molecules of [VO{*N*-(2-oxido-1-naphthylmethylene)-L-ala}OBu^s-(HOBu^s)], **2**. The configurations at the centres of chirality are noted. The broken line indicates the (weak) bond to the oxygen of butanol. Selected bond lengths (Å) and angles (°): V(1)–O(1) 1.604(9), VC(2)–O(7) 1.584(8), V(1)–O(2) 1.940(8), V(2)—O(8) 1.958(6), V(1)–O(4) 1.863(7), V(2)–O(10) 1.873(7), V(1)–O(5) 1.759(8), V(2)–O(11) 1.754(8), V(1)–O(6) 2.328(8), V(2)—O(12) 2.302(8), V(1)–N(1) 2.101(7), V(2)–N(2) 2.101(9), O(2)–C(14) 1.302(12), O(8)–C(36) 1.279(14), O(3)–C(14) 1.197(12), O(9)–C(36) 1.229(12), O(1)–V(1)–O(6) 173.4, O(7)–V(2)–O(12) 172.7(3), O(1)–V(1)–O(2) 97.8(4), O(7)–V(2)–O(8) 96.7(3), O(1)–V(1)–O(4) 98.0(4), O(7)–V(2)–O(10) 99.5(4), O(1)–V(1)–O(5) 103.5(4), O(7)–V(2)–O(11) 103.8(4), N(1)–V(1)–O(1) 96.2(3), N(2)–V(2)–O(7) 95.1(4).

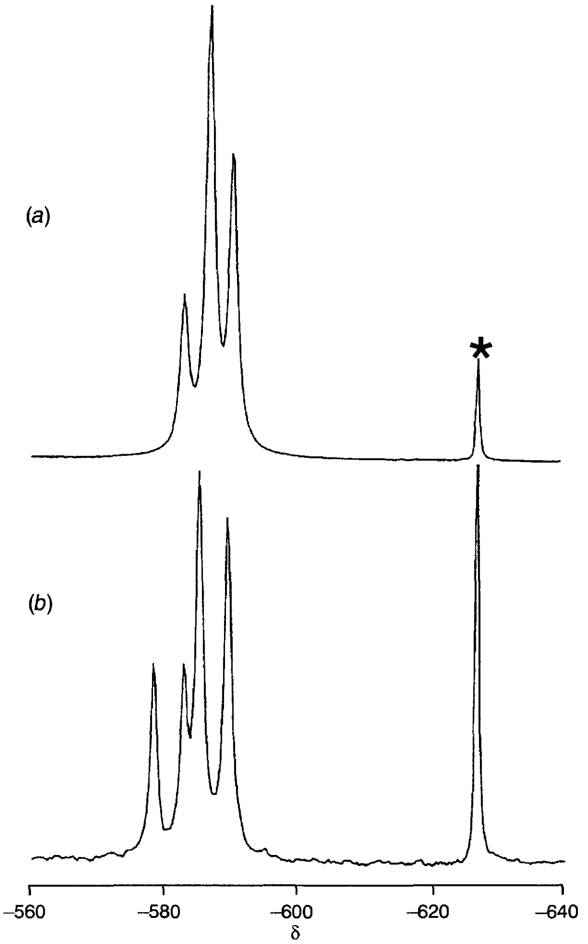

Fig. 2 94.7 MHz ^{51}V NMR spectra of [VO{*N*-(2-oxido-1-naphthylmethylene)-L-ala}OBu^s(HOBu^s)], **2**, (*a*), and [VO(sal-L-ala)OBu^s(HOBu^s)] (*b*), dissolved in CD_2Cl_2/*sec*-butyl alcohol 0.7/0.3 *v*/*v*. The signal at high field [δ(^{51}V) −627] indicated by * is a product of alcoholysis [VO(OBu^s)$_3$]. Other chemical shifts δ(^{51}V) [relative to δ ($VOCl_3$) 0]: (*a*): −583.0, −586.8, −590.2; *b*: −578.9, −583.4, −585.6, −589.8.

isomers might be present: (*i*) there may be coincidence in position within experimental line widths; (*ii*) the formation of particular diastereoisomers may be disfavoured; (*iii*) ligated HOsBu may dissociate off the complex in solution, leaving a five-coordinate complex with three centres of chirality. At the present state, it cannot be decided, whether the same diastereoisomers found in the solid material are also present in solution.

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Footnotes

† Preparation of **2**: 250 mg (0.55 mmol) of **1**, prepared according to ref. 9 and stored under nitrogen, was dissolved in 5 ml of butan-2-ol plus CH_2Cl_2 (*ca.* 0.5 ml) to improve the solubility of **1**. After complete dissolution, the CH_2Cl_2 was removed under reduced pressure and air was bubbled through the remaining solution for 2 h to form a red–brown solution of **2**. This was concentrated *in vacuo* until the first solid particles appeared at the surface. After standing overnight, crystalline **2** had separated. The volume of the solution was slowly reduced for several hours, resulting in an increase in crystal size and amount of compound **2**. The crystals were finally filtered off and sucked dry. Yield: 45%. Satisfactory elemental analysis. ν_{max}/cm^{-1} (KBr) 3235 (broad, OH), 1696 and 1655 (asym. carboxylate), 1622 and 1608 (C=N), 1340 (sym. carboxylate), 988 and 973 (V=O).

The complex [VO(sal-L-ala)OBu^s(HOBu^s)] has been prepared accordingly and gave a satisfactory elemental analysis.

‡ *Crystal data*: $C_{22}H_{30}NO_6V$, M = 455.41 g mol^{-1}, monoclinic, space group $P2_1$, a = 10.642(2), b = 12.284(3), c = 17.450(6) Å, β = 91.39(2)°, Z = 4, V = 2280.5(11) Å^3, D_c = 1.326 g cm^{-3}, F(000) = 960, μ(Mo-Kα) = 4.7 cm^{-1}. Final $R1$ = 0.052 ($wR2 = \sqrt{[\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]}$ = 0.1196) for 2329 reflections with $I > 2\sigma(I_o)$ measured in the θ range 2.27 to 22.54° at 153 K on a Hilger & Watts diffractometer. Residual electron density: max. 0.275, min. −0.210 e Å^{-3}. 548 parameters were refined. The refinement was carried out with SHELXL-93. In order to circumvent unresolvable disorder problems with the carbon atoms C(17), C(21), C(22) and C(38), these were treated with one of the temperature factors fixed. Hydrogen atoms were calculated into ideal positions and refined with isotropic temperature factors. The absolute configuration has been checked (the Flack parameter is zero) and corresponds, as far as the L-alanine fragment is concerned, with the expected one. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at he Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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