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Study on the isomerism in *meso*-amavadin and an amavadin analogue

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Abstract

An X-ray crystallographic study of '*meso*-amavadin' revealed that in the crystal the negatively charged anionic species of the title compound join into infinite hydrogen-bonded chains, counterbalanced by cationic hydronium species. Along with water of crystallization a three-dimensional hydrogen-bonded network is formed. Based on NMR- and X-ray data of amavadin and '*meso*-amavadin', a model was developed that accounts for the structure of amavadin-type complexes, i.e. vanadium(IV) non-oxo complexes that contain two ligands with a tridentate *N*-hydroxyiminodiacetate backbone. The model describes the different arrangements of the two ligands around the vanadium and it accounts for eventual symmetry in the complex. The model was used for the interpretation of NMR-data of an amavadin analogue with a benzyl group at the ligand backbone.

Keywords: Amavadin; Vanadium; Crystal structure; Secondary hydroxylamine; *N*-Hydroxyimino-(2,2′)-dipropionic acid

1. Introduction

One of the most prominent examples of a vanadium-containing natural compound is amavadin. In 1972, Bayer et al. isolated this compound from the mushroom *Amanita muscaria* [1,2]. After the identification of the amavadin ligand as (2*S*,2′*S*)-*N*-hydroxyimino-2,2′-dipropionic acid **1** [3,4], it was evident that it formed a 2:1 complex with vanadium(IV) (Fig. 1). In 1987, Bayer and coworkers [5] postulated that amavadin exists as an octa-coordinated vanadium non-oxo compound, a so-called 'bare' vanadium species. However, no X-ray structure could be obtained [5,6].[1] It took until 1999 [7,8] for single crystal X-ray studies to be reported. These concerned amavadin crystallized as its Ca^{2+} salt $[\Delta\text{-}VL_2]^{2-}$ $[Ca(H_2O)_5]^{2+} \cdot 2H_2O$. They confirmed the 'bare' vanadium(IV) in an octa-coordinated complex (**2**).

The amavadin-system has been explored further via the preparation and crystallographic determination of analogous structures [9–17]. In most of these cases, the natural ligand **1** or its simplest achiral analogue **3** was complexed to the early transition metals Ti, Zr, Nb, Ta and Mo. In one particular case, a ligand with ethyl groups on the backbone was prepared (**4**) and its complexation with V and Mo was studied [14,17]. In all cases, the structures obtained were octa-coordinated non-oxo metal compounds like amavadin.

The reported crystallographic determinations of amavadin and its analogues all concern the deprotonated forms. This leaves the question unanswered whether protonated amavadin **2** has a similar structure. In particular, the location of the protons either on the acid groups or on water molecules can have a significant influence on the structure. Following our enantioselective synthesis of the optically pure (*S*,*S*)-amavadin ligand [18], we attempted to crystallize the protonated form of amavadin, but were not successful.

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[1] The X-ray determination of natural amavadin has been mentioned in the literature (Ref. [17]), but the authors of [17] refer to unpublished work.

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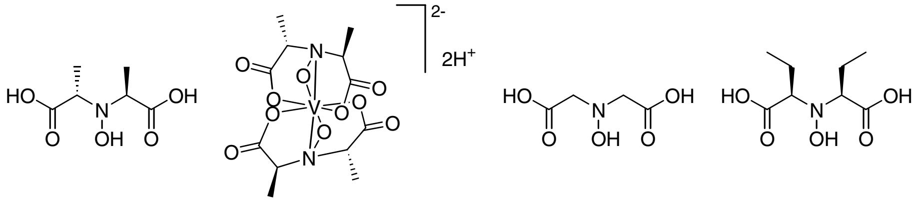

1
H_3L
ligand of amavadin

2
$V^{IV}L_2H_2$
amavadin

3

4

Fig. 1. Amavadin and its ligand analogues.

Therefore, we also included amavadin prepared from the *meso*-ligand in our studies.[2] This afforded the corresponding amavadin stereoisomer, which we named '*meso*-amavadin'. Evaporation of an aqueous solution of '*meso*-amavadin' yielded crystals immediately.

Herein we present the X-ray crystallographic determination of '*meso*-amavadin', a stereoisomer of the natural compound amavadin. Based on the NMR- and X-ray data of amavadin-type vanadium complexes, we propose a model that accounts for the isomerism that is present in these complexes. Secondly, we applied this model to interpret the NMR-data of an amavadin analogue containing a benzyl group at the ligand backbone.

2. Materials and methods

2.1. General considerations

^1H, ^{13}C and ^{51}V NMR spectra were recorded on a Varian VXR-400S (400 MHz) or a Varian Unity Inova 300 (300 MHz) instrument. Chemical shifts of the ^1H and ^{13}C nuclei are expressed in parts per million (δ) relative to tetramethylsilane. Chemical shifts of the ^{51}V nuclei are expressed in parts per million (δ) relative to the external reference $VOCl_3$. Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet). Low-resolution mass spectroscopy was measured on a Micromass Quattro LC-MS spectrometer (Electron Spray Ionization). High resolution mass spectroscopy was measured on a Thermo LTQ Orbitrap; resolution 50,000; mass accuracy <2 ppm; samples were diluted with a 1:1 methanol/water solution; injection volume: 10 µl; flowrate: 50 µl/min; eluent is a 1:1 methanol/water solution. Optical rotations were obtained using a Perkin–Elmer 241 polarimeter. Melting points were measured on a Büchi 510 and are uncorrected. $VO(acac)_2$ was recrystallised from acetone [19] prior to use. All other chemicals and dry solvents were obtained from Aldrich or Merck and were used as received. Other solvents were purchased from Baker. Ultrapure water (MilliQ) was used.

2.2. Synthesis of '*meso*-amavadin' = (Δ,Λ)-(OC-6-1′3)-diaquahydrogen-hydrogen(bis((R-1-carboxy-κO-ethyl)-(S-1-carboxy-κO-ethyl)-η^2-azanolato)vanadium(IV)) dihydrate

To a solution of 31 mg (0.119 mmol) of $VO(acac)_2$ in methanol was added an aqueous solution of 42 mg (0.237 mmol) of the *meso*-ligand. After stirring for 30 min, the mixture was clear and dark blue. All volatiles were removed by rotary evaporation, and the blue residue was redissolved in 2 mL of water. Evaporation of the water initially yielded a crystalline blue solid, while after thorough drying 47 mg of a purple powder was obtained (0.117 mmol, 99%). Mp: decomposes. MS (*m*/*z*) 402.5 (ES^+, M+1), 803.2 (ES^+, 2M+1), 400.5 (ES^-, M−1), 801.3 (ES^-, 2M−1). The powder was redissolved in water, the solution was concentrated and left to crystallize at 4 °C.

2.3. Crystal structure determination

A blue crystal was used for data collection on a Nonius KappaCCD diffractometer on rotating anode with Mo Kα radiation at 150 K. Crystal data: $C_{12}H_{17}N_2O_{10}V \cdot H_5O_2 \cdot 2(H_2O)$, Monoclinic, $P2_1/c$, $a = 11.8487(12)$ Å, $b = 10.7262(12)$ Å, $c = 15.6163$ Å, $\beta = 92.682(14)°$, $V = 1982.5(4)$ Å^3. A total of 53,421 reflections up to $\Theta = 27.5°$ were measured and averaged into a unique set of 4516 reflections ($R_{int} = 0.068$). The structure was solved by Direct Methods (SHELXS86 [20]) and refined with SHELXL97 [21] to $R = 0.0346$ for 3580 reflections with $I > 2\sigma(I)$, $wR2 = 0.0858$, $S = 1.02$, residual density excursions between −0.33 and 0.34 e/Å^3. H-atoms on carbon were introduced at calculated positions and refined riding on their carrier atoms. Hydrogen atoms on oxygen were identified from difference Fourier maps and their positions refined. An $[O_2H_5]^+$ cation was positively identified in a contoured map. Another contoured map involving the short H-bond between O2 and O8 indicated a disordered H-atom position with the major component near O8. No attempt was made to refine a disorder model. Illustrations and structure validation were done with PLATON [22]. CCDC 624773 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html.

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[2] T. Hubregtse, U. Hanefeld, I.W.C.E. Arends, Eur. J. Org. Chem. (2007), accepted for publication.

2.4. Oxidation of 'meso-amavadin' to $[\mathrm{VL}_2]^-[\mathrm{PPh}_4]^+$ = (OC-6-1′3)-tetraphenylphosphonium(bis((R-1-carboxy-κO-ethyl)-(S-1-carboxy-κO-ethyl)-η^2-azanolato)vanadium(V))

The oxidation and isolation were carried out according to the procedure reported earlier for amavadin [18]. ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$) δ; 1.66 (d (doublet), 6H, $\mathrm{CH}\mathit{H}_3$, $J = 7.3$ Hz), 1.68 (d, 6H, $\mathrm{CH}\mathit{H}_3$, $J = 7.3$ Hz), 4.80 (q (quartet), 2H, $\mathrm{C}\mathit{H}\mathrm{CH}_3$, $J = 7.3$ Hz), 5.06 (q, 2H, $\mathrm{C}\mathit{H}\mathrm{CH}_3$, $J = 7.3$ Hz), 7.65, 7.77, 7.92 (m (multiplet), 20H, $\mathrm{P(C_6}\mathit{H}_5)_4$). ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$) δ; 173.39, 172.17 (4C, $\mathit{C}\mathrm{OOH}$), 135.84 (4C, $\mathrm{P}(\mathit{C}_6\mathrm{H}_5)_4$), 134.39 (8C, $\mathrm{P}(\mathit{C}_6\mathrm{H}_5)_4$), 130.75 (8C, $\mathrm{P}(\mathit{C}_6\mathrm{H}_5)_4$), 117.46 (d, 4C, P–$C$, $^1J_{\mathrm{P–C}} = 89$ Hz), 72.31, 71.55 (4C, $\mathit{C}\mathrm{HCH}_3$), 19.00 (4C, $\mathrm{CH}\mathit{C}\mathrm{H}_3$). ^{51}V NMR (79 MHz, $\mathrm{CDCl_3}$, 25 °C) δ; −257.

2.5. Synthesis of **6** = (OC-6-1′3)-dihydrogen(bis((carboxy-κO-methyl)(1-carboxy- κO-2-phenyl-ethyl)-η^2-azanolato)vanadium(IV))

To a solution of 40 mg (0.168 mmol) of **5** in 15 ml of ethanol was added 21 mg (0.080 mmol) of $\mathrm{VO(acac)_2}$. The mixture immediately coloured deep brown for a few seconds. After stirring for 20 min, the mixture was clear and blue–purple and the smell of Hacac was noticed. All volatiles were removed by rotary evaporation and the residue was stripped twice with methanol. The dry residue was then washed twice with dichloromethane, yielding 41 mg (0.078 mmol, 98%) of **6** as a glittering blue solid. Mp = 130 °C (decomp). $[\alpha]_\mathrm{D}^{20} = -6.0°$ ($c = 0.4$, $\mathrm{H_2O}$). HRMS–ESI (High Resolution Mass Spectrometry–Electrospray Ionization) calcd. for $\mathrm{C_{22}H_{23}N_2O_{10}}$ $[\mathrm{M+H}]^+$ 526.0787, found 526.0788. HRMS–ESI calcd. for $\mathrm{C_{22}H_{21}N_2O_{10}}$ $[\mathrm{M-H}]^-$ 524.0641, found 524.0639.

2.6. Synthesis of 7 by the oxidation of **6**

The oxidation of **6** and the isolation of **7** were carried out according to the procedure reported earlier for amavadin [18], except that $\mathrm{MgSO_4}$ was used as a drying agent instead of $\mathrm{CaCl_2}$. Due to the non-racemic ligand, diastereoisomers are formed in a ratio of A:B = 3:4. The assignment of the ^{1}H and ^{13}C resonances was based on this ratio. ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz, 25 °C) δ; 3.02–3.12 (m, 4H, $\mathrm{C}\mathit{H}_2\mathrm{C_6H_5^A} + \mathrm{C}\mathit{H}_2\mathrm{C_6H_5^B}$), 3.60–3.83 (m, 8H, $\mathrm{C}\mathit{H}_2\mathrm{C_6H_5^A} + \mathrm{C}\mathit{H}_2\mathrm{C_6H_5^B} + \mathrm{NC}\mathit{H}_2^\mathrm{A} + \mathrm{NC}\mathit{H}_2^\mathrm{B}$), 4.15 (d, 1H, $\mathrm{NC}\mathit{H}_2^\mathrm{B}$, $J = 15.9$ Hz), 4.23 (d, 1H, $\mathrm{NC}\mathit{H}_2^\mathrm{A}$, $J = 16.2$ Hz), 4.43 (d, 1H, $\mathrm{NC}\mathit{H}_2^\mathrm{A}$, $J = 15.9$ Hz), 4.48 (d, 1H, $\mathrm{NC}\mathit{H}_2^\mathrm{B}$, $J = 16.2$ Hz), 4.93 (dd (double doublet), 1H, $\mathrm{NC}\mathit{H}^\mathrm{A}$, $J =$ 2.4 Hz and $J = 11.4$ Hz), 5.01 (dd, 1H, $\mathrm{NC}\mathit{H}^\mathrm{B}$, $J = 2.4$ Hz and $J = 11.4$ Hz), 5.23 (dd, 1H, $\mathrm{NC}\mathit{H}^\mathrm{B}$, $J = 2.4$ Hz and $J = 11.4$ Hz), 5.27 (dd, 1H, $\mathrm{NC}\mathit{H}^\mathrm{A}$, $J = 2.4$ Hz and $J =$ 11.4 Hz), 7.22–7.35 (m, 20H, $\mathrm{C_6}\mathit{H}_5^{\mathrm{A+B}}$), 7.65, 7.77, 7.92 (m, 40H, $\mathrm{P(C_6}\mathit{H}_5)_4^{\mathrm{A+B}}$). ^{13}C NMR ($\mathrm{CDCl_3}$, 75 MHz, 25 °C): δ 172.11$^\mathrm{B}$, 172.09$^\mathrm{A}$, 171.18$^{\mathrm{A+B}}$, 171.01$^\mathrm{A}$, 170.96$^\mathrm{B}$, 169.93$^\mathrm{B}$, 169.89$^\mathrm{A}$ (8C, $\mathit{C}\mathrm{OOH}$), 137.88$^\mathrm{A}$, 137.86$^\mathrm{B}$, 137.57$^\mathrm{B}$, 137.55$^\mathrm{A}$, 129.45$^\mathrm{B}$, 129.42$^\mathrm{A}$, 129.04$^\mathrm{A}$, 129.00$^{\mathrm{B+B}}$, 128.94$^\mathrm{A}$, 127.81$^\mathrm{A}$, 127.78$^\mathrm{B}$ (24C, $\mathit{C}_6\mathrm{H}_5$), 136.12 (8C, $\mathrm{P}(\mathit{C}_6\mathrm{H}_5)_4^{\mathrm{A+B}}$), 134.65 (16C, $\mathrm{P}(\mathit{C}_6\mathrm{H}_5)_4^{\mathrm{A+B}}$), 130.97 (16C, $\mathrm{P}(\mathit{C}_6\mathrm{H}_5)_4^{\mathrm{A+B}}$), 117.72 (d, 8C, P–$C^{\mathrm{A+B}}$, $^1J_{\mathrm{P–C}} = 89$ Hz), 78.58$^\mathrm{B}$, 78.46$^\mathrm{A}$, 78.00$^\mathrm{A}$, 77.93$^\mathrm{B}$ (4C, $\mathrm{N}\mathit{C}\mathrm{HC_6H_5}$), 66.42$^\mathrm{A}$, 66.32$^\mathrm{B}$, 65.54$^\mathrm{A}$ + B (4C, $\mathrm{N}\mathit{C}\mathrm{H_2}$), 39.57$^\mathrm{A}$, 39.54$^\mathrm{B}$, 39.51$^\mathrm{B}$, 39.49$^\mathrm{A}$ (4C, $\mathit{C}\mathrm{H_2C_6H_5}$). ^{51}V NMR (79 MHz, $\mathrm{CDCl_3}$, 25 °C) δ; −230.

3. Results and discussion

3.1. X-ray structure of 'meso-amavadin'

The vanadium surrounding in the crystal structure of '*meso*-amavadin' (Fig. 2) is similar to that reported earlier for the $\mathrm{Ca^{2+}}$ salt of the naturally occurring amavadin [7]. The four unidentate carboxylates constitute the equatorial $\mathrm{VO_4}$-plane and the two N–O groups bind side-on above and below the plane. The two ligands coordinate in a meridional fashion to the octa-coordinated vanadium center.

The asymmetric unit contains a vanadium complex with the composition $[\mathrm{VL_2H}]^-$, which means that formally one of the ligands has two deprotonated carboxylate groups and the other ligand has one deprotonated and one protonated carboxylate group. A more detailed analysis suggests that each ligand is partially protonated at O8 and O2, respectively. Both atoms form a relatively short hydrogen bond with O···O = 2.503(2) Å. The associated coordinating O1 and O6 have a distance to $\mathrm{V_1}$ that is in the order of 0.04 Å longer than the corresponding distances for the deprotonated carboxylate groups (Fig. 2). In addition, the asymmetric unit contains two molecules of water and a hydronium (i.e. $[\mathrm{H_2O–H–OH_2}]^+$) cluster. An O···O distance of 2.446(2) Å is characteristic for such a species. Thus, four molecules of water are present per vanadium. Hydrogen bridges connect the asymmetric units into an infinite threedimensional network, whereby only one short hydrogen bridge forms a direct link between neighboring vanadium complexes. The unit cell contains four vanadium complexes, that are pairwise exact mirror images and linked into infinite chains (Fig. 3).

3.2. Proposed model to account for the isomerism and symmetry in amavadin-type complexes

It has previously been demonstrated that the vanadium atom of amavadin is chiral and that the complex exists as Δ and Λ diastereomers [7].[3] Furthermore, the vanadium atom is configurationally labile in solution and the complex is prone to epimerization [18,23,24]. The interconversion between Δ and Λ diastereomers occurs via a flip of one

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[3] For a definition for the assignment of Δ and Λ chiral descriptors to metal complexes, see: G.J. Leigh (Ed.) Nomenclature of Inorganic Chemistry, Recommendations 1990, Blackwell Scientific Publications, Oxford, 1990.

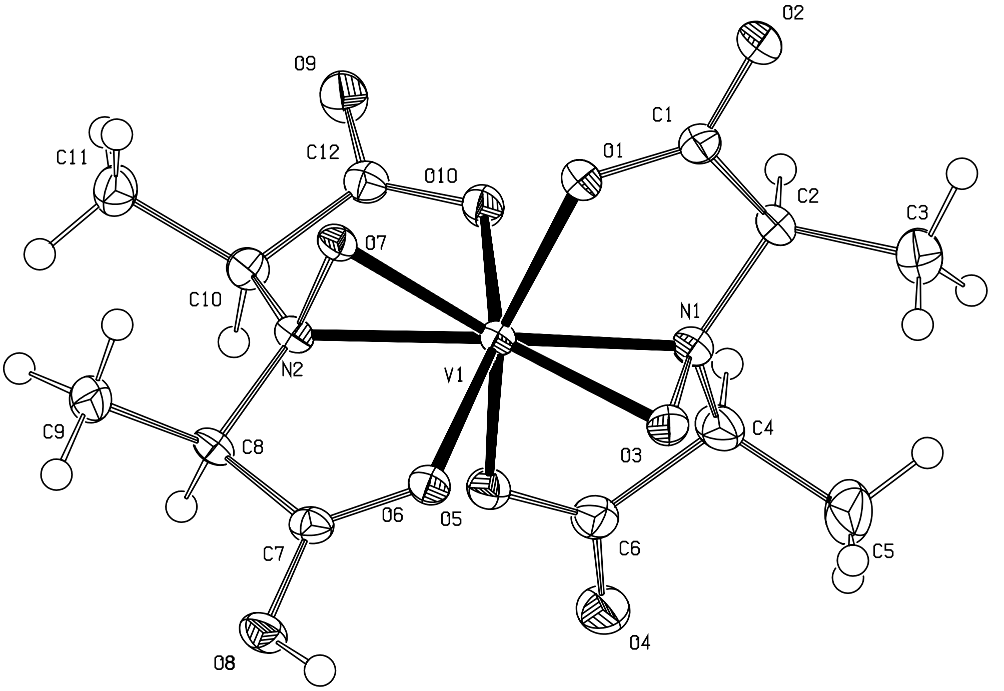


Fig. 2. ORTEP view of the ‘*meso*-amavadin’ anion. Displacement ellipsoids are drawn at the 50% probability level. The hydronium cation and water molecules are not shown. Selected distances Å: V1–O3 = 1.9599(12), V1–O7 = 1.9675(12), V1–N1 = 2.0220(16), V1–N2 = 2.0337(15), V1–O5 = 2.0304(13), V1–O10 = 2.0252(13), V1–O1 = 2.0662(13), V1–O6 = 2.0846(13).

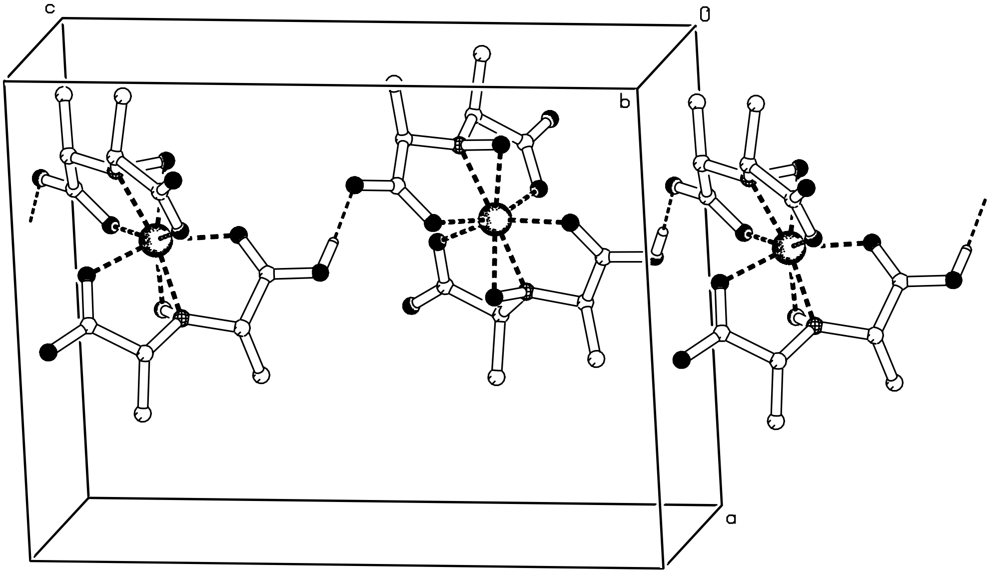


Fig. 3. Infinite hydrogen-bonded chain of the title anion and its mirror image. Hydrogen bonding with the hydronium cation and water molecules is not shown.

of the N–O moieties (Fig. 4), which results in mirrored positions of the carboxylates and the *N*–O groups while the directions of the methyl groups on the two chiral ligands are not mirrored. When viewed axially, the staggered methyl groups in the Λ isomer (Ra and Rb) point towards the equatorial direction, while the staggered methyl groups in the Δ isomer (Rb and Rc) point towards the axial direction. The axial representation also reveals C_2-symmetry with respect to an equatorial axis of rotation, which is in accordance with the observation that the four propionate units in the complex result in two different sets of signals in the ^{1}H and ^{13}C NMR of oxidized amavadin (Fig. 5a) [18,23]. It has previously been shown that only minimal structural changes take place upon the one-electron oxidation to vanadium(V) when the amavadin ligand **1** [7,24] or its analogues **3** [15,24] and **4** [17] are complexed

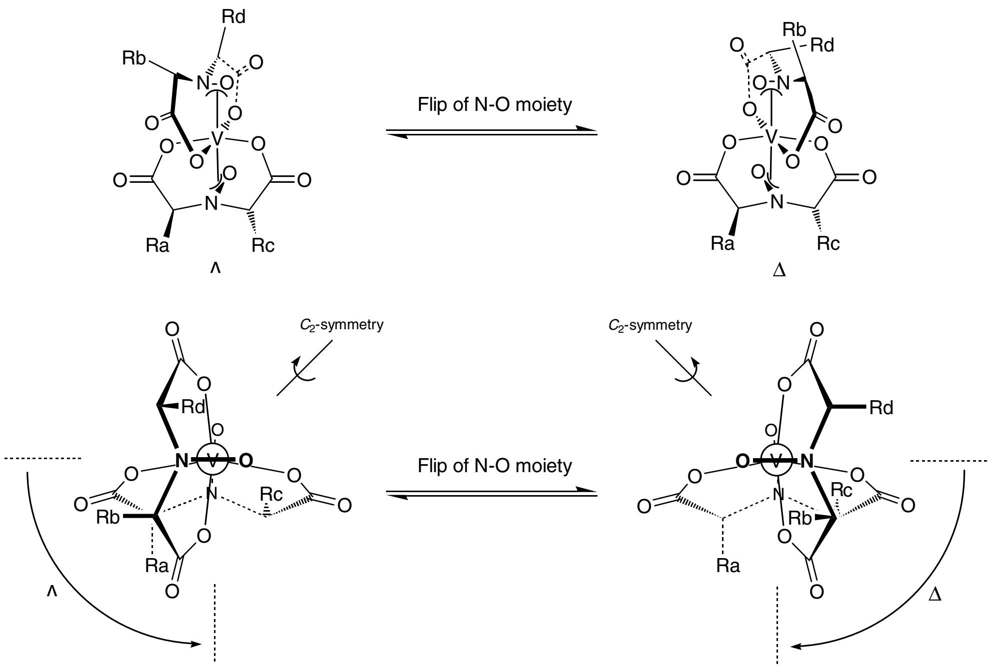


Fig. 4. Equatorial (VO_4-plane) and axial representations of the Λ and Δ diastereomers of amavadin that account for the symmetry in the complex and the assignment of the Λ and Δ chiral descriptors.

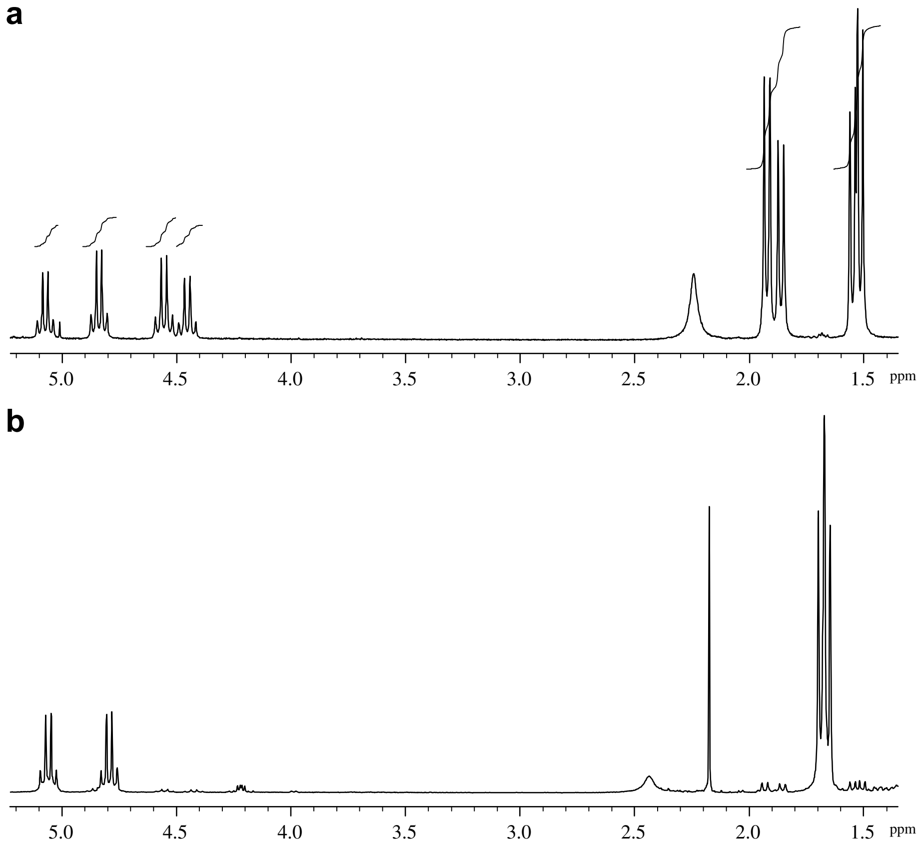
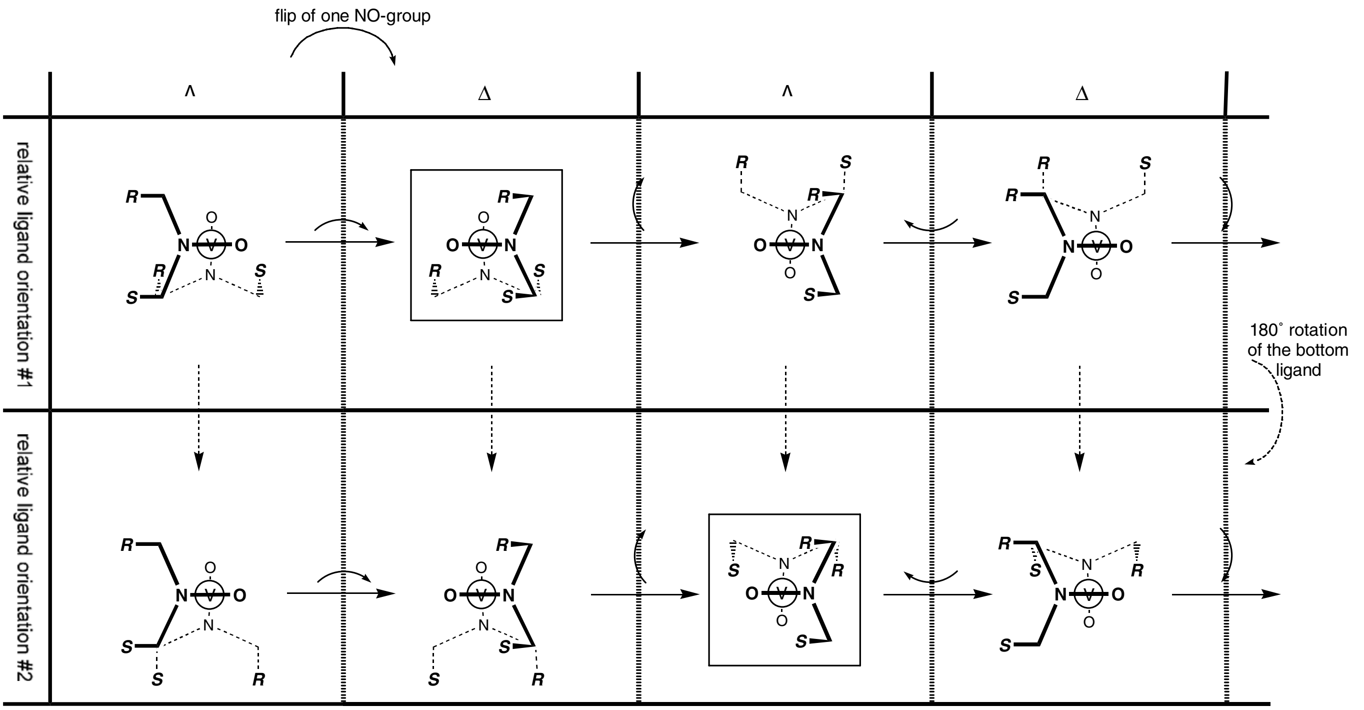


Fig. 5. ^1H NMR spectra of oxidized amavadin (a) and oxidized '*meso*-amavadin' (b).

to vanadium. It has thus been demonstrated that NMR measurements of the vanadium(V) complexes are also a valid tool to discuss the properties of the vanadium(IV) complexes.



Scheme 1. There are eight possibilities to arrange the two *meso*-ligands around the vanadium (wedged bonds indicate axial methyl groups, non-wegded bonds indicate equatorial methyl groups).

In '*meso*-amavadin' the situation appeared to be more complicated because the presence of (*R*) and (*S*) stereogenic centers in the ligands breaks the symmetry of the molecule. This results in eight different possibilities to arrange the two *meso*-ligands around the vanadium, instead of the two possibilities for the (*S*,*S*)-ligands. In Scheme 1 these are shown schematically from the axial point of view. The configurations of the four backbone carbons are given by the letters ***R*** and ***S*** (located at the respective methyl groups) and the carboxylates are omitted for clarity. It can be seen that the two different relative ligand orientations are not reached by flipping of the N–O moieties, but that they require a 180° rotation of the entire ligand around the N–O bond.

In the crystal structure of '*meso*-amavadin', all the methyl groups occupy the axial directions (Fig. 2).[4] There are two structures in Scheme 1 that also have the 'all-axial' conformation (highlighted). They are mirror images (enantiomers) that have an axis of C_2-symmetry and they correspond to the two mirrored vanadium complexes in the symmetric unit of the crystal structure. To investigate whether the solution structure is identical with the crystal or whether more isomers exist in solution, an NMR-study was performed analogously to those of amavadin: the '*meso*-amavadin' was oxidized, and the resulting vanadium(V) complex was isolated as its PPh_4-salt. The NMR of '*meso*-amavadin' showed two doublets and two quartets in the ^1H NMR (Fig. 5b) and six resonances in the ^{13}C NMR (two signals for each of the three propionate carbons). When comparing the ^1H NMR spectrum of oxidized amavadin with that of oxidized '*meso*-amavadin' in Fig. 5, it is self-evident that the first consists of two diastereomers and the latter of two enantiomers. The absence of other signals in the NMR of oxidized '*meso*-amavadin' demonstrated that a C_2-symmetrical structure is present in solution.[5] In addition to the two highlighted 'all-axial' conformations in Scheme 1, there are two other conformations with C_2-symmetry (shown in the lower left and upper right corners of Scheme 1). In contrast, these have an 'all-equatorial' conformation. They can, therefore, be excluded because all the methyl substituents would then occupy the less-favourable positions close to the carboxylates of the other ligand. There is consequently a great certainty that the solution structure is identical with the crystal structure.

Scheme 1 shows that the existence of two different relative orientations contributes to the constitution of the eight different ligand arrangements around the vanadium. A change in this relative orientation would require an (imaginary) 180° rotation of the entire ligand around the N–O bond, whereby the two carboxylates change their positions in the equatorial VO_4-plane. This involves their de- and reconnection, a process that is not likely to occur in view of the high stability constants of the complex [5]. The constitution of the two different ligand orientations most likely

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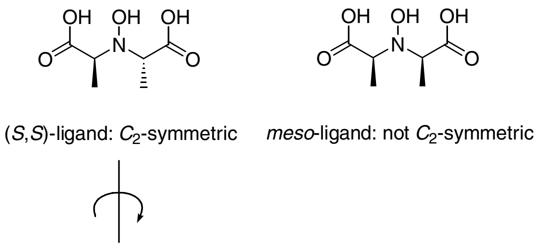
[4] The reported crystal structure of the vanadium(IV) complex with *meso*-ligand **4** also has the 'all-axial' conformation [17].

[5] The singlet at 2.17 ppm is due to a trace of acetone.

finds its origin in the ligand complexation during the synthesis of the complex, and can therefore be interpreted as the existence of two modes in which a second ligand can connect to an (imaginary) intermediate mono-ligand complex. This reveals a fundamental difference in how the two Δ and Λ isomers of amavadin and '*meso*-amavadin' are constituted. Moreover, this also implies that the configuration of the vanadium in '*meso*-amavadin' is non-labile, and that – in principle – the isolation of either one of its enantiomeric forms is possible. The fundamental reason for this is that the (*S*,*S*)-ligand is C_2-symmetric, while the *meso*-ligand is not (Fig. 6). The imaginary 180° rotation would result in an identical structure in case of the (*S*,*S*)-ligand, and in a different structure in the case of the *meso*-ligand. This explanation reveals generality, because the C_2-symmetry of the ligand can also be broken when it carries two different backbone substituents. This results in a model that covers the main aspects of the isomerism in vanadium complexes with amavadin-type ligands. In addition, a solid interpretation of the NMR-data of such complexes should be possible because the symmetry is also accounted for in the model. To test this hypothesis, an amavadin analogue was prepared from a ligand that contains two different backbone substituents.

3.3. Testing the model

Analogue **5** of the natural amavadin ligand was synthesized, which differs in the groups attached to the backbone: it has one backbone hydrogen atom of **3** substituted by a benzyl group and is therefore chiral.[2] A slightly enantiomerically enriched **5** was employed for the complexation of vanadium. The vanadium(IV) complex **6** was prepared analogously to the synthesis of amavadin [18]. The increased hydrophobicity of **5** relative to the natural ligand **1** allowed its use in an excess of 5–10%, since it could be washed out with dichloromethane after the complexation. High resolution electrospray mass spectrometry of the new complex confirmed its identity as **6**. The characterization with NMR was performed in analogy to the studies with **1** [18]: **6** was oxidized in water using $(NH_4)_2Ce(NO_3)_6$ and the resulting vanadium(V) species was extracted into dichloromethane with PPh_4Br to yield the $[VL_2]^-[PPh_4]^+$ complex **7** (Scheme 2).



(*S*,*S*)-ligand: C_2-symmetric *meso*-ligand: not C_2-symmetric

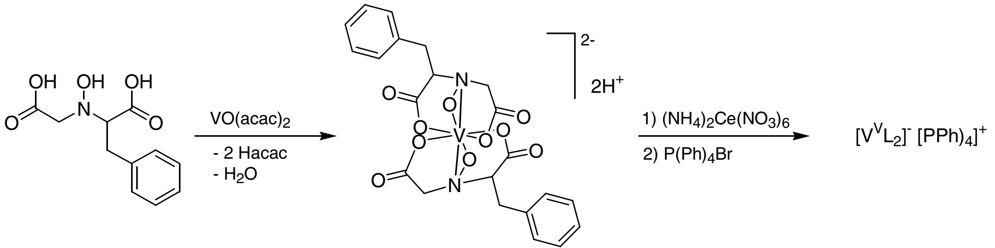
Fig. 6. The (*S*,*S*)-ligand is C_2-symmetric, but the *meso*-ligand is not.

3.3.1. NMR-studies of 7

We used the model to predict the appearance of **7** in the NMR, which is described below. Due to the chiral center in the ligand, it offers three combinations with vanadium: (1) two (*R*)-ligands (2) two (*S*)-ligands and (3) one (*R*)- and one (*S*)-ligand. In analogy to Scheme 1, two of the eight possible ligand arrangements of each combination have the 'all-axial' conformation, which results in the presence of **7** as six isomers: **7a**–**f** (Fig. 7). These isomers consist of the enantiomeric pairs **7a** + **7d**, **7b** + **7c** and **7e** + **7f**, which are indicated by the double-headed arrows. The representations in Fig. 7 also demonstrate that **7a**–**d** have an axis of C_2-symmetry, while **7e** and **7f** are non-C_2-symmetric species.

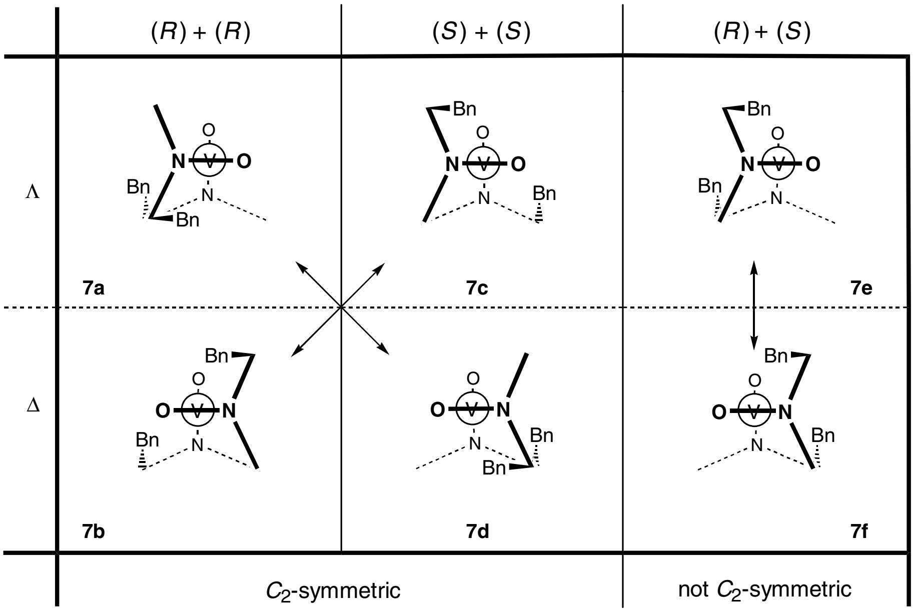
In the NMR, the four C_2-symmetric species **7a**–**d** are expected to account for half of the signals, while the two non-C_2-symmetric species **7e** and **7f** account for the other half. Because of the use of a slightly enantiomerically enriched **5**, half of the signals of **7** will have a lower integral. The ratio between these integrals is related to the enantiomeric ratio of the ligand as shown in Fig. 7.

Fig. 8 shows the ^1H NMR of **7**. The signals of the phenyl group are well separated from the aromatic protons of the PPh_4-counterion (not shown), while the other signals show moderate overlap. It can clearly be seen that the proton in the $NCHCH_2$ fragment couples with the two benzylic protons, resulting in a double doublet with coupling constants of $J = 2.4$ and $J = 11.4$ Hz. These values can be expected in rigid systems such as **7**. All protons are represented by four resonances each, which can most clearly be seen for the $NCHCH_2$ protons that are represented by four double doublets. This is also the case in ^{13}C NMR, which shows most resonances grouped per two signals that are very close to each other, or as one signal of higher intensity: there are



5 **6** **7**

Scheme 2. Preparation of the amavadin analogue **6** and its oxidation to **7**.



relative abundances of the isomers of **7**:	
If (R) : (S) = x : y, then	(R)+(R) : (S)+(S) : (R)+(S) = x^2 : y^2 : 2xy

Fig. 7. Amavadin analogue **7** is present as six isomers. The three enantiomeric pairs are indicated by the arrows, their relative abundances are given below.

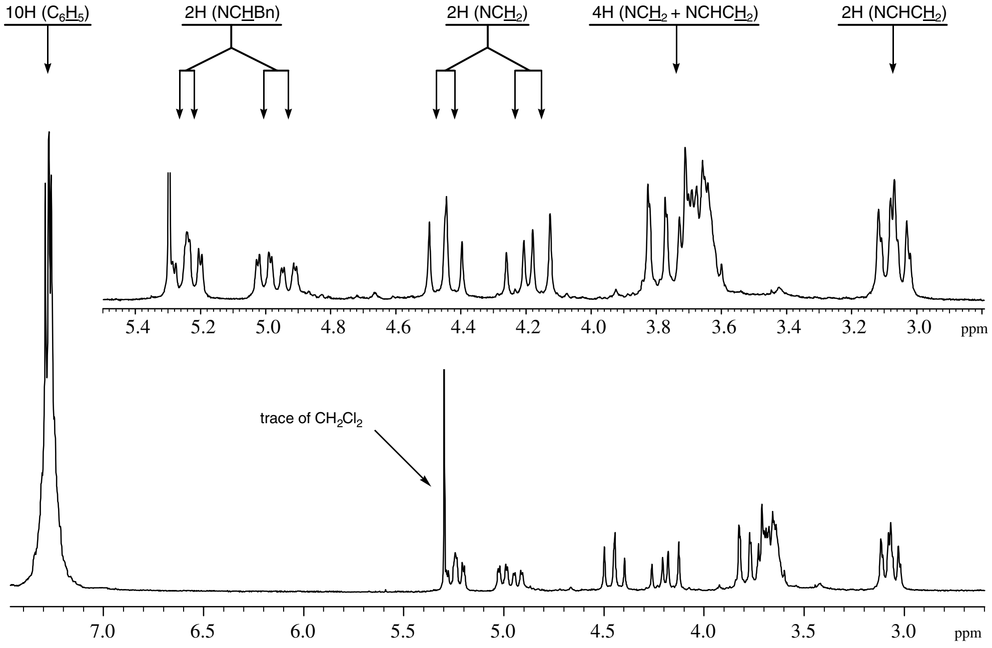


Fig. 8. The ^{1}H NMR of complex **7**.

2 + 1 + 2 + 2 signals for the carboxylate carbons, 2 + 2 signals for the two methenyl backbone carbons, 2 + 2 signals for the two methylene backbone carbons and 2 + 2 signals for the two benzylic carbons. Furthermore, in both the ^{1}H and ^{13}C NMR all signals are present in an approximate 3:4 ratio of signal intensity.

The proposed presence of the three diastereomers is confirmed by the NMR data of **7** and the observed 3:4 integral ratio confirms the slight enantiomeric enrichment of the ligand. As in amavadin, it was observed that **7**, although it is a mixture of diastereomers, gives only one signal in the ^{51}V NMR (−230 ppm).

4. Conclusions

We performed the synthesis and X-ray crystallographic study of '*meso*-amavadin', which revealed to be anionic in the crystal with a hydronium cluster as counter ion. Based on NMR- and X-ray data of amavadin and '*meso*-amavadin', we developed a model that accounts for the structure of amavadin-type complexes, i.e. vanadium(IV) non-oxo complexes that contain two ligands with a tridentate *N*-hydroxyiminodiacetate backbone. The model is based on two properties of the complex: (1) the configurationally labile vanadium and (2) the existence of two different relative ligand orientations. It explains how these properties result in different modes to arrange the two ligands around the vanadium and it accounts for eventual symmetry in the complex. We demonstrated that the model can be used to predict the ^{1}H and ^{13}C NMR spectra of an amavadin analogue that contains a benzyl group at the ligand backbone.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jinorgbio.2007.02.006.

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