doi:10.2533/chimia.2019.96 Chimia 73 (2019) 96–97

Chemical Education

A CHIMIA Column

Topics for Teaching: Chemistry in Nature

The Fungus *Amanita muscaria*: From Neurotoxins to Vanadium Accumulation

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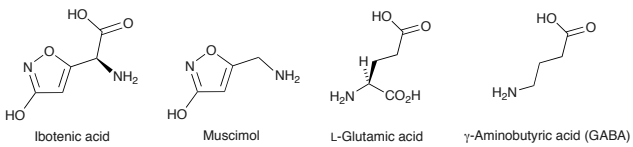
Abstract: The fungus *Amanita muscaria* contains neurotoxins which account for its long-time use as a hallucinogen. In contrast, *A. muscaria* is also a bioaccumulator of high levels of vanadium, the reason for which is still obscure.

Keywords: Amavadin · Bioinorganic · Chemical education · Chirality · Fungus · Neurotoxins · Vanadium

The fungus *Amanita muscaria* is instantly recognisable by its appearance (Fig. 1) and is an iconic image in fairy stories. Known as the *fly agaric* fungus (*Fliegenpilz* in German, *l'amanite tue-mouches* in French, *Ovolaccio* in Italian), it is poisonous although poisoning in humans rarely leads to death.[1] After ingestion of the fungus, a human starts to experience symptoms after 30 minutes: visual and hearing sensations, space distortion, unawareness of time, and dilation of the pupils. These effects last for a few hours, followed by drowsiness and finally deep sleep accompanied by vivid dreams. Usually after about 8 hours, the episode ends with complete recovery.[1] These effects have led to *A. muscaria* having a long history as a hallucinogen. The effects are also called the *pantherina–muscaria syndrome*, because of the similar effects observed with both the *Amanita* species *A. pantherina* (the *panther cap*) and *A. muscaria*. These should not be confused with so-called 'magic mushrooms' or 'shrooms' which are fungi of the genus *Psilocybe*.

Fig. 1. Two stages in the growth of the fungus *Amanita muscaria*. ©Edwin C. Constable 2017

The origins of *A. muscaria* poisoning lie in the neurotoxins ibotenic acid and muscimol (Scheme 1). Both are derivatives of the heterocycle isoxazole. Ibotenic acid mimics the stimulatory brain neurotransmitter L-glutamic acid (Scheme 1), while muscimol mimics the inhibitory neurotransmitter γ-aminobutyric acid (GABA or 4-aminobutanoic acid).[2] Ibotenic acid acts as an excitatory neurotoxin in contrast to the depressive effects of GABA. After ingestion of *A. muscaria*, ibotenic acid and muscimol are rapidly absorbed by the body. The dominant effects on a mammal of ingesting the fungus are agitation and confusion, consistent with ibotenic acid being the dominant neurotoxin present.[3] The name *fly agaric* arises from a traditional use of extracting neurotoxins and using the extract for controlling flies in farming communities.[4]



Scheme 1. Structures of the neurotoxins ibotenic acid and muscimol, and of the neurotransmitters glutamic acid and GABA.

Quite distinct from its neurotoxic properties, *A. muscaria* is also fascinating in being a bioaccumulator of vanadium. Living organisms accumulate metals for a range of biochemical functions, but the accumulation of large amounts of vanadium is very unusual. Although vanadium is an essential trace metal, it is usually present in organisms in very low concentrations, typically 0.11 mg in an average 70 kg human. The natural abundance of vanadium in the Earth's crust is around 160 ppm.[5] *A. muscaria* fungi contain up to 400 times more vanadium than is typical of plants and fungi. A number of other *Amanita* fungi also accumulate vanadium, and the metal is transported and stored in the form of the vanadium(IV) coordination complex *amavadin* (also spelled *amavadine*). Levels of vanadium of more than 10^3 to 10^4 times the concentration typical in soil have been found.[6] Amavadin contains the complex anion $[VL_2]^{2-}$ (Fig. 2) in which the ligand L^{3-} is the conjugate base of (*S,S*)-2,2'-(hydroxyimino) dipropionic acid (Fig. 2, left). The single crystal structure of the calcium salt $[Ca(OH_2)_5][VL_2]$ was determined in 1999.[7]

The $[VL_2]^{2-}$ complex contains five stereogenic centres: two in each ligand (Fig. 2, left) and the vanadium(IV) centre. Each L^{3-} ligand acts as a tetradentate donor. It is the relative orientations of the two N–O units (Fig. 3) that render the vandanium centre stereogenic by giving the coordination complex a right- (labelled *Δ*) or left- (labelled *Λ*) handedness (Fig. 4). *A. muscaria* contains an approximate 1 : 1 mixture of the two diastereoisomers of amavadin.

Before continuing with the *A. muscaria* story, it is instructive to clarify why we are describing the *Δ*- and *Λ*-forms of amavadin

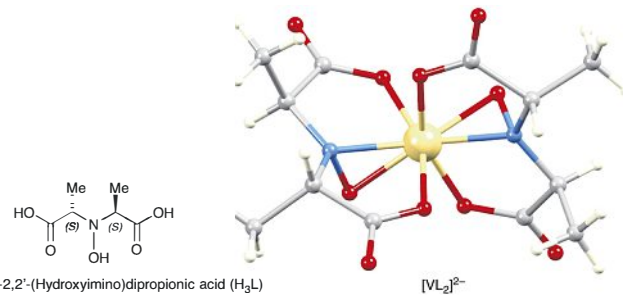


Fig. 2. Structures of the conjugate acid H_3L of the ligand that binds vanadium(IV) in amavadin, and the crystallographically determined structure of Δ-$[VL_2]^{2-}$ in $[Ca(OH_2)_5][VL_2]$.[7–9]

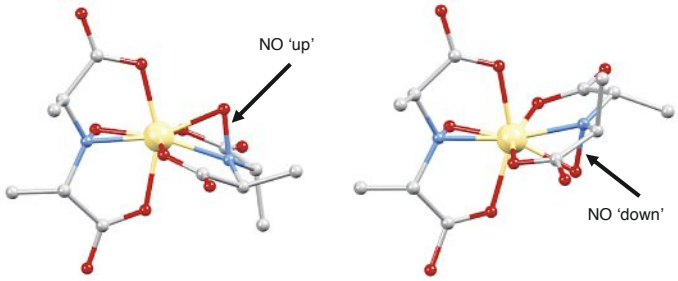


Fig. 3. The relative orientations of the N–O units in the two ligands is the origin of the Δ- and Λ-metal centres in amavadin (see Fig. 4). In the representations of the two structures, the left-hand ligand is identically positioned. Hydrogen atoms omitted for clarity.

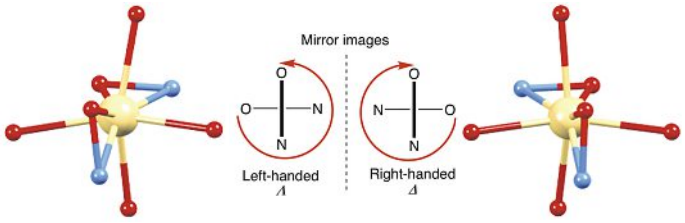


Fig. 4. Focus on the arrangements of the two N–O units to define the Δ- and Λ-metal centres in amavadin.

as *diastereoisomers* and not as *enantiomers*. Enantiomers are non-superposable mirror images, and indeed in Fig. 4, the Δ- and Λ-arrangements of the two N–O units are shown as mirror images. However, in amavadin, the ligand L^{3-} is derived from the (*S*,*S*)-2,2'-(hydroxyimino)dipropionic acid in which the stereochemistry at the stereogenic centres is defined (Figs. 2 and 3). Inversion at all five stereogenic centres in amavandin would have to be observed to produce enantiomers of the complex.

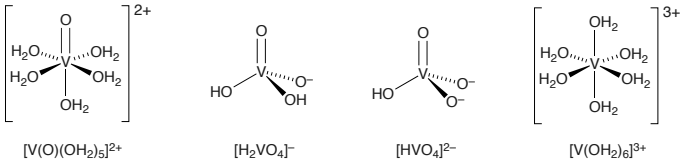
The reasons why *A. muscaria* accumulates such high concentrations of vanadium and the role of amavadin remain unanswered questions. However, in its oxidized vanadium(V) form (Eqn. 1) amavadin shows catalytic behaviour, being able to function as a catalase in the absence of a biological thiol RSH (Eqn. 2) or as a peroxidase in the presence of a thiol (Eqn. 3).[6,10] (A catalase is an enzyme that catalyses the decomposition of hydrogen peroxide to dioxygen and water, and a peroxidase catalyses the one-electron oxidation of a substrate by hydrogen peroxide.) In Eqns 1–3, the oxidized and reduced forms of amavadin are abbreviated as $\{V^V\}$ and $\{V^{IV}\}$, respectively, and the hydrogen peroxide required is produced by the fungus.[11] Typically, peroxidases are haem proteins (*i.e.* iron-containing) and in fungi, they are involved in cross-linking thiol groups in proteins. The vanadium-based amavadin is less efficient than haem peroxidases.[10]

$$\{V^{IV}\} + H_2O_2 + 2H^+ \rightarrow \{V^V\} + 2H_2O \quad (1)$$

$$4\{V^V\} + 4H_2O_2 \rightarrow 4\{V^{IV}\} + 3O_2 + 2H_2O + 4H^+ \quad (2)$$

$$2\{V^V\} + 2RSH \rightarrow 2\{V^{IV}\} + RS{-}SR + 2H^+ \quad (3)$$

Amavadin demonstrates some unusual features for a vanadium(IV) complex because it combines a high coordination number of eight, *N,O*-donor ligands and high stability in aqueous media.[10] A coordination number of eight is unusual for a first row *d*-block metal ion. It is more typical for vanadium(IV) to occur as an oxido species, for example in $[V(O)(OH_2)_5]^{2+}$ (Scheme 2).



Scheme 2. Structures of some vanadium species involved in vanadium bioaccumulation in sea squirts (*Ascidia*).

Two other types of organism accumulate high levels of vanadium: marine polychaeta fan worms and ascidians such as the sea squirts *Ascidia nigra* and *Ascidia gemmata* in which the concentration of vanadium is up to 10^7 times greater than in the surrounding seawater. Uptake of vanadium is in the form of $[H_nVO_4]^{(3-n)-}$ ($n = 1$ or 2, Scheme 2). Vanadium(V) is then reduced to vanadium(IV) in $[V(O)(OH_2)_5]^{2+}$, and the metal is stored in the blood cells (*vanadocytes*) as vanadium(III), probably in the form of $[V(OH_2)_6]^{3+}$ (Scheme 2) or $[V(OH_2)_5(HSO_4)]^{2+}$.[6] In this series of vanadium complexes, the higher oxidation state species contain oxido ligands which are more typical than the *N,O*-donor ligands found in amavadin.

In this column, we have highlighted two independent properties of the fungus *A. muscaria*. First, the fungus is poisonous because of the presence of neurotoxins. Second, it can accumulate extremely high concentrations of vanadium, the reasons for which remain obscure.

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