

## Model Complexes for Amavadine, a Vanadium Natural Product

MOHD. ASRI NAWI and THOMAS L. RIECHEL\*

Department of Chemistry, Miami University, Oxford, Ohio 45056, U.S.A.

Received May 18, 1984

### Abstract

Amavadine is a vanadium natural product from the mushroom *Amanita muscaria*. Earlier reports have characterized the compound as a vanadyl ( $\text{VO}^{2+}$ ) complex with two N-hydroxy- $\alpha$ -iminodipropionic acid ligands, but no hypothesis as to its function has yet been put forward. We report here the synthesis, isolation, and properties of bis(iminodiacetato)oxovanadium(IV) and bis( $\alpha$ -iminodipropionato)oxovanadium(IV). The complex bis( $\beta$ -iminodipropionato)oxovanadium(IV) has been prepared in solution. These complexes serve as models for Amavadine. The structures of the models are analogous to that of Amavadine, with two bidentate, singly charged ligands bonding through one oxygen and one nitrogen atom. The visible spectra suggest the possibility of 1:1 complexes in solution in addition to the 2:1 ligand to metal complexes. Preliminary electrochemical data suggest reversible  $\text{V(IV)} \rightleftharpoons \text{V(III)}$  couples.

### Introduction

The natural occurrence of vanadium in biological systems is now well documented and a few species have even been shown to require this metal for proper growth and reproduction [1]. Nonetheless, a specific function has not been identified for any vanadium natural product. Recently, Nielsen [2] and Macara [3] have suggested some possible roles for vanadium, but in almost all cases the immediate environment of the metal, that is, the ligands or bonding atoms, is unknown.

In only one case has a vanadium natural product been isolated [4]. Bayer and Kneifel reported that the mushroom *Amanita muscaria* had a vanadium content as high as 120 ppm (dry weight) [5]. They later characterized a vanadium extract from the mushroom, a vanadyl ( $\text{VO}^{2+}$ ) complex with two N-hydroxy- $\alpha$ -iminodipropionic acid ligands. They

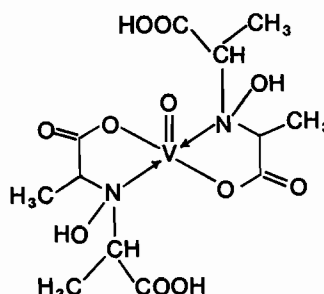


Fig. 1. The structure of Amavadine as proposed by Kneifel and Bayer.

named the natural product Amavadine [6] and proposed the structure shown in Fig. 1. These authors reportedly synthesized a similar complex for verification of the structure. We have been unable to reproduce this synthesis, and no other reports on Amavadine or its synthetic analogue have appeared in the literature.

Numerous studies have been reported on the solution chemistry of simple vanadium amino acid complexes, but few compounds have been isolated. We report here the first isolation of vanadium compounds with iminodiacid ligands including iminodiacetic acid and  $\alpha$ -iminodipropionic acid (ligands I and II, respectively, in Fig. 2). Complex formation in solution with  $\beta$ -iminodipropionic acid will also be discussed (Fig. 2, ligand III). These complexes serve as models for Amavadine since the metal–ligand stoichiometry, bonding, and geometry is similar. This report will focus on the synthesis and stoichiometry of these compounds. Since the natural function of Amavadine may involve redox processes, preliminary electrochemical results will also be presented.

### Experimental

#### Reagents and Solvents

High purity dimethylsulfoxide (DMSO) and acetonitrile (AN) were obtained from Burdick and Jackson Laboratories and used as received as electrochemical

\* Author to whom correspondence should be addressed.

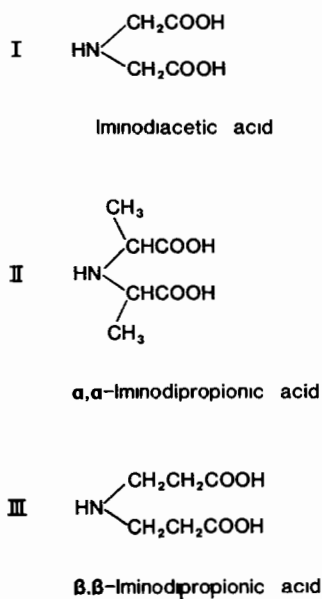


Fig. 2. Ligands for Amavadin model complexes.

solvents. Tetraethylammonium perchlorate (TEAP) was prepared from tetraethylammonium bromide (Aldrich) and perchloric acid as previously described [7] and was the supporting electrolyte for the above solvents. Tetraethylammonium hydroxide (TEAOH) was obtained from Aldrich as a 25% solution in water. Vanadyl sulfate was obtained from Fisher Scientific or Aldrich. Vanadyl perchlorate,  $\text{VO}(\text{ClO}_4)_2 \cdot 5\text{DMSO}$ , was prepared by the literature method [8].

#### Preparation of Ligands

Iminodiacetic acid (ligand I) was obtained from Aldrich and recrystallized from a methanol–water mixture.

Preparation of  $\alpha,\alpha$ -iminodipropionitrile (the precursor of  $\alpha,\alpha$ -iminodipropionic acid) was based on Dubsy's method [9]. A 200 ml ether solution containing 22 g (0.5 mol) of acetaldehyde was added slowly to a 75 ml aqueous solution of 27.5 g (0.5 mol) of ammonium chloride. After this reaction mixture was completely chilled, 32.5 g (0.5 mol) of potassium cyanide in 75 ml of water was added with stirring. After being shaken for 5 hours 32 g (0.5 mol) of acetic acid was added. A second 22 g of acetaldehyde in ether and 32.5 g of KCN (aqueous) was added and the mixture again shaken for 5 hours. The ether layer was removed, the aqueous layer was extracted twice with ether, and all ether layers were combined. The resulting ether solution was chilled in a dry ice–isopropanol bath and the white product which precipitated was collected by filtration. The crude product was recrystallized from ether giving a yield of about 20 g (33%). *Anal.*

calc. for  $\text{C}_6\text{H}_9\text{N}_3$ , C 58.52%, H 7.37%; found: C 58.46%, H 7.39%.

$\alpha,\alpha$ -Iminodipropionitrile was converted to the acid by base hydrolysis. About 7 g (0.05 mol) of the dinitrile was dissolved in 1 l of water and added dropwise to a hot stirred solution of barium hydroxide octahydrate (32 g (0.1 mol) in 100 ml of water). The solution was stirred for 4 hours with the temperature maintained at 90–95 °C. The excess barium was precipitated by bubbling  $\text{CO}_2$  through the solution and the  $\text{BaCO}_3$  was removed by filtration. The aqueous solvent was then stripped off leaving a syrupy liquid. Upon addition of ethanol the barium salt,  $\text{Ba}[\text{NH}(\text{CH}(\text{CH}_3)\text{COO})(\text{CH}(\text{CH}_3)\text{COOH})_2]$  was obtained in 70% yield. This barium salt (10 g, 0.034 mol) was dissolved in 300 ml of water and an equimolar amount of  $\text{H}_2\text{SO}_4$  was added with stirring. The  $\text{BaSO}_4$  precipitate was filtered off and the solvent was stripped from the filtrate. Absolute ethanol was added to the resultant yellow liquid and precipitation of white crystals began after scratching the walls of the flask. Approximately 5 g (90% yield) of the purified  $\alpha,\alpha$ -iminodipropionic acid was obtained. *Anal.* calc. for  $\text{C}_6\text{H}_{11}\text{NO}_4$ , C 44.72%, H 6.83%; found: C 44.55%, H 6.87%.

$\beta,\beta$ -Iminodipropionic acid was prepared by basic hydrolysis of  $\beta,\beta$ -iminodipropionitrile (Eastman Kodak Chemicals) by the method of Ford [10].

#### Synthesis of Complexes

##### *Bis(iminodiacetato)oxovanadium(IV)*

Two procedures were used to make this complex.

**Procedure A** In this procedure the ligand is first converted to the barium salt,  $\text{Ba}[\text{NH}(\text{CH}_2\text{COO})(\text{CH}_2\text{COOH})_2]$ , as described by Dubsy [9] for the  $\alpha,\alpha$ -iminodipropionic acid ligand. About 1.3 g (0.01 mol) of iminodiacetic acid was dissolved in 40 ml of water. To this was added 1.6 g (0.005 mol)  $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$  dissolved in 80 ml of water. The mixture was heated to 80–90 °C and stirred for 3 hours. The barium salt was not isolated, but rather 1 g (0.005 mol)  $\text{VOSO}_4 \cdot 3\text{H}_2\text{O}$  in 20 ml of water was added dropwise. The  $\text{BaSO}_4$  precipitate was filtered off leaving a purple–blue solution. The volume was reduced yielding a crude blue solid upon addition of alcohol. The precipitate was collected and purified from acetonitrile as a blue powder. *Anal.* calc. for  $\text{VO}(\text{C}_8\text{H}_{12}\text{N}_2\text{O}_8) \cdot 2\text{H}_2\text{O}$ , C 26.16%, H 4.36%, N 7.63%, found: C 25.93%, H 4.38%, N 7.56%. After drying under vacuum at 110 °C water was lost. *Anal.*: calc. for  $\text{VO}(\text{C}_8\text{H}_{12}\text{N}_2\text{O}_8)$ , C 29.01%, H 3.63%, N 8.46%; found: C 28.69%, H 3.65%, N 8.25%.

**Procedure B** In the first step vanadyl acetate was made from vanadyl chloride. About 2.9 g (0.02 mol) of  $\text{VOCl}_2$  (a deliquescent solid) was put into a

50 ml beaker (no solvent). To this was added 2 g (0.024 mol) of anhydrous sodium acetate dissolved in 25 ml of absolute methanol. The mixture was stirred and chilled, and then the sodium chloride precipitate was filtered off leaving a blue-green solution of vanadyl acetate. In a separate step, 3.2 g (0.024 mol) of iminodiacetic acid was suspended in 100 ml of methanol. This solution was heated and a minimum amount of water was added to dissolve the ligand. The vanadyl acetate solution was added dropwise to the hot solution of ligand resulting in a purple-blue solution. Since the product is soluble in methanol, a frozen slurry (dry ice-isopropanol bath) of the complex in methanol was filtered quickly and a blue powder was recovered. The crude product was purified from acetonitrile. *Anal.*: calc. for  $\text{VO}(\text{C}_8\text{H}_{12}\text{N}_2\text{O}_8) \cdot \text{H}_2\text{O}$ , C 27.51%, H 3.44%, N 8.02%; found: C, 27.47%, H 3.55%, N 7.68%.

*Bis*( $\alpha$ -iminodipropionato)oxovanadium(IV)  
Dihydrate

This compound was prepared by Procedure A described above using  $\alpha$ -iminodipropionic acid,  $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ , and  $\text{VOSO}_4 \cdot 3\text{H}_2\text{O}$ . In this case, though, the product did not precipitate upon addition of alcohol. The solvent was stripped off and the crude product was purified in acetonitrile. After heating under vacuum the dihydrate was obtained. *Anal.*: calc. for  $\text{VO}(\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_8) \cdot 2\text{H}_2\text{O}$ , C 34.04%, H 5.67%, N 6.62%; Found: C 34.14%, H 5.76%, N 6.59%. Synthesis of this compound via Procedure B gave a mixture of products.

*Instrumentation*

The electrochemical instrumentation, cells, and electrodes used for the experiments performed in non-aqueous solvents have been described previously in this journal [11]. For the aqueous studies, a Princeton Applied Research Model 303 Static Mercury Drop Electrode was interfaced to the PAR Model 173 potentiostat and Model 175 Universal Programmer. The Model 303 SMDE incorporates a Ag/AgCl reference electrode.

Spectrophotometric measurements were made on a Cary Model 14 UV/vis spectrophotometer and a Perkin Elmer Model 683 IR spectrometer and data station.

**Results and Discussion**

*Synthesis and Properties*

The synthesis of vanadyl iminodiacetic complexes was achieved by the following reactions:

Procedure A

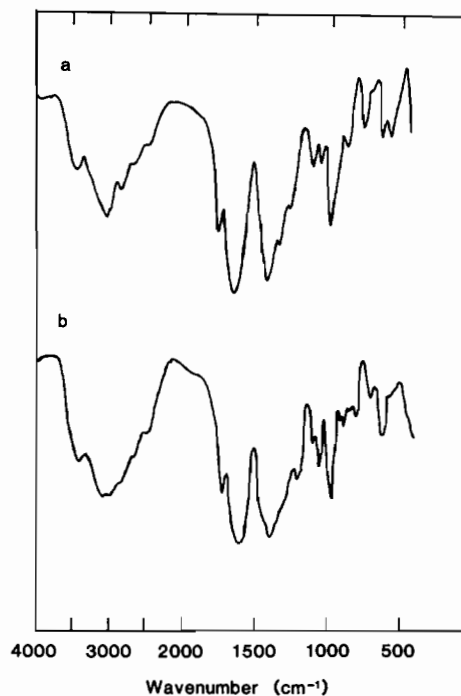
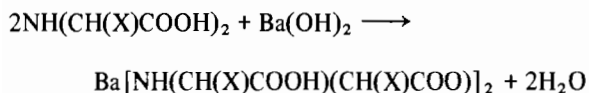
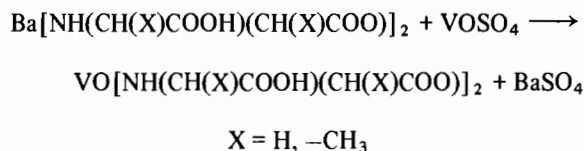
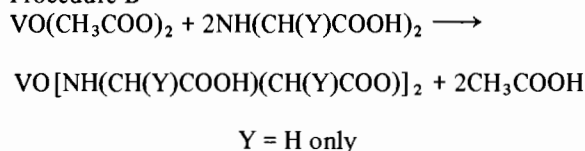


Fig. 3. IR spectra in KBr of (a) bis(iminodiacetate)oxovanadium(IV) and (b) bis( $\alpha$ , $\alpha$ -iminodipropionato)oxovanadium(IV).



Procedure B



Procedure A worked well for both iminodiacetic acid and  $\alpha$ -iminodipropionic acid ligands. Procedure B gave a pure product only for the iminodiacetic acid ligand. Neither procedure worked for the  $\beta$ -iminodipropionic acid ligand, but complex formation did occur with this ligand in solution (see below)

Bis(iminodiacetato)oxovanadium(IV) was obtained in three forms, namely the dihydrate, the monohydrate and the anhydrous form. The compounds were light blue in color, air stable and were soluble only in water. The low pH ( $\sim 2.5$ ) of an aqueous solution and the two equivalence points observed in the titration with NaOH are consistent with the presence of two protonated carboxylic acid groups in the complex.

Bis( $\alpha$ -iminodipropionato)oxovanadium(IV) was isolated as the dihydrate. Heating under vacuum did not remove the coordinated water molecules. Its properties were similar to the iminodiacetato complex in color, acidity, and air stability. The compound was soluble in water, methanol, ethanol and DMSO.

The infra-red spectra of bis(iminodiacetato)oxovanadium(IV) and bis( $\alpha$ -iminodipropionato)oxovanadium(IV) recorded in KBr pellets are shown in Figs. 3a and 3b, respectively. The spectra are quite similar. The diacetate complex showed a broad band covering the region 3600–2500  $\text{cm}^{-1}$ . Five overlapping peaks occurred at 3400, 3100, 2850, 2700 and 2500  $\text{cm}^{-1}$ . Similar peaks were observed for the dipropionate complex and in both complexes these peaks are due to various O–H, N–H, and C–H stretching modes. Bands in this region have also been reported for water hydrogen bonded to an amine group [12]. Thus, a water molecule may be bound as  $\text{H}_2\text{O}\cdots\text{HNRR}'$  in these compounds. Two carbonyl stretching bands are observed at 1725 and 1617  $\text{cm}^{-1}$  for the diacetate complex and at 1710 and 1617  $\text{cm}^{-1}$  for the dipropionate complex. The bands at 1725 and 1710  $\text{cm}^{-1}$  verify the existence of non-coordinated carboxyl groups in the complexes. The peaks at 1617  $\text{cm}^{-1}$  are due to C=O when the carboxylate group is coordinated [13, 14], in this case to the metal center. The band at 1411  $\text{cm}^{-1}$  for the diacetate complex and that at 1382  $\text{cm}^{-1}$  for the dipropionate complex are assigned as C–O single bond stretching modes [12]. Finally, proof of the existence of  $\text{VO}^{2+}$  in each compound is established by the bands at 968  $\text{cm}^{-1}$  (diacetate complex) and 961  $\text{cm}^{-1}$  (dipropionate) complex. These bands correspond to the V=O stretch as reported for numerous vanadyl compounds [15].

#### Electrochemistry

A cyclic voltammogram of 10 mM bis(iminodiacetato)oxovanadium(IV) in aqueous 0.1 M KCl is shown in Fig. 4a. The potential scan range was limited by the oxidation of mercury at about 0.0 V vs. a Ag/AgCl reference electrode. On the first cathodic scan a broad reduction peak is observed at  $-1.00$  V overlapping a sharper peak at  $-1.25$  V. (These peaks become more distinct on the second scan.) On the reverse scan, oxidation peaks occur at  $-1.15$ ,  $-0.95$ , and  $-0.55$  V. Based on multiple scan data the peaks at  $-1.25$  and  $-1.15$  V may correspond to a reversible couple.

The cyclic voltammogram of  $\text{VOSO}_4$  in water (not shown) gave only two peaks: a reduction at  $-1.18$  V and an oxidation at  $-0.55$  V. These are the same as the peaks in Fig. 4b. Figure 4b is the voltammogram of a 1:3 mol ratio mixture of  $\text{VOSO}_4$  and iminodiacetic acid. A cyclic voltammogram of the ligand alone showed a reduction peak at  $-1.80$  V.

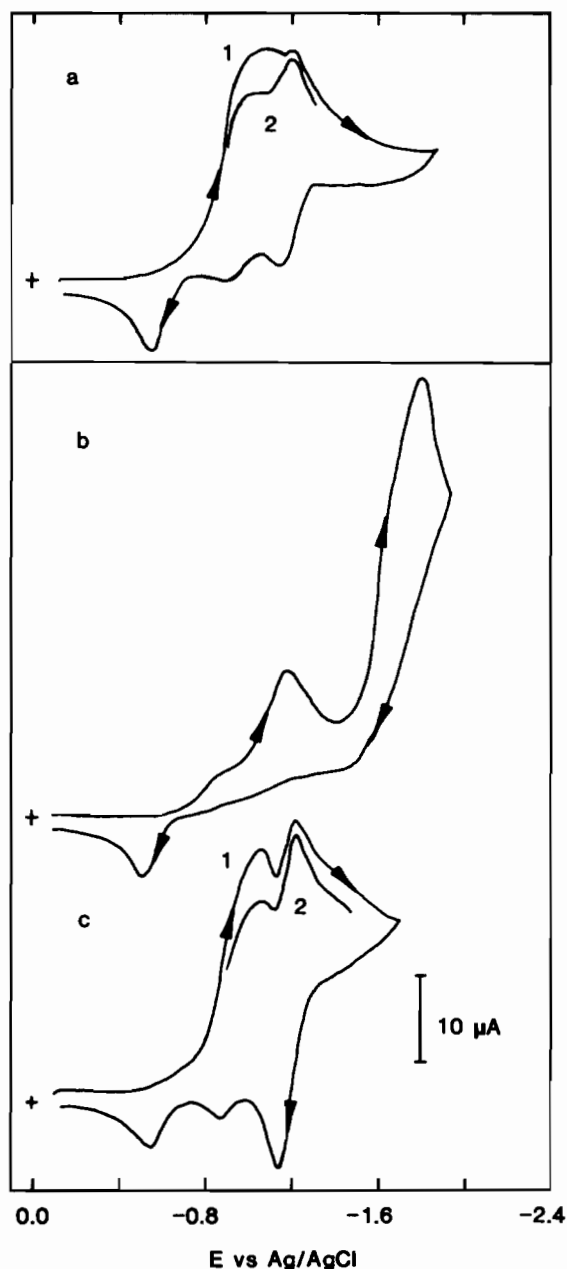


Fig. 4. Cyclic voltammograms in 0.1 M aqueous KCl of (a) 10 mM bis(iminodiacetato)oxovanadium(IV), (b) a mixture of 10 mM  $\text{VOSO}_4$  and 30 mM iminodiacetic acid, and (c) solution (b) with 30 mM NaOH added. Scan rate 0.2 V/sec.

Thus, no complex is formed under the conditions of Fig. 4b. When NaOH was added in a 1:1 mol ratio to the ligand, the voltammogram shown in Fig. 4c was observed. Clearly, upon deprotonation the ligand complexes with vanadium and gives a voltammogram nearly identical to that of the isolated product (Fig. 4a). These data suggest that the peaks at  $-1.25$  and  $-1.15$  V are a reversible couple corresponding to the reduction and subsequent oxidation of the complex. Both Figs. 4a and 4c suggest that some dissociation

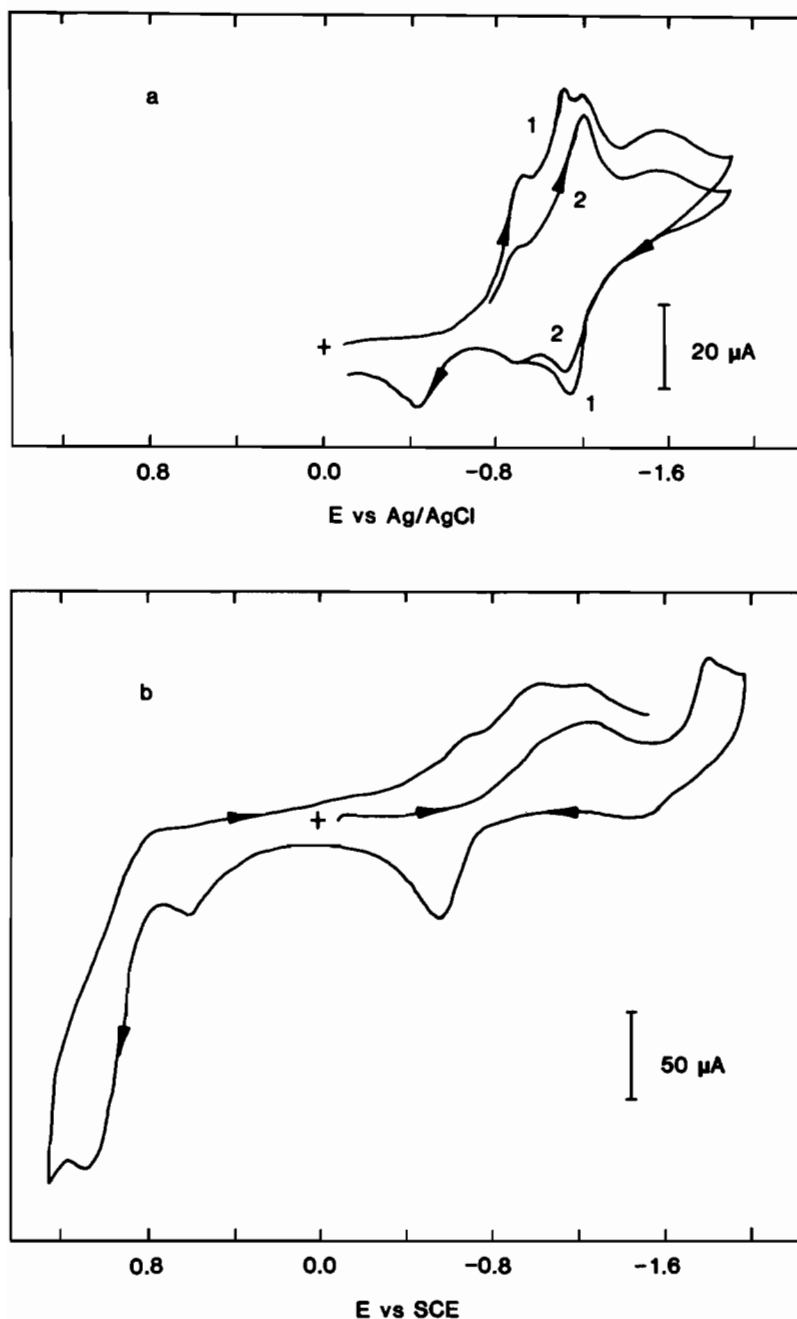


Fig. 5 Cyclic voltammograms of bis( $\alpha$ -iminodipropionato)oxovanadium(IV). (a) 10 mM complex in 0.1 M aqueous KCl. (b) 3 mM complex in 0.1 M TEAP/DMSO. Scan rate 0.2 V/sec

of the complex occurs. 'Free' vanadyl ion (or perhaps  $\text{VO}(\text{H}_2\text{O})_5^{2+}$ ) is reduced at  $-1.18$  V, followed by a subsequent oxidation at  $-0.55$  V. There may be another complex corresponding to the broad reduction peak near  $-1.00$  V and its subsequent oxidation may occur at  $-0.95$  V.

As shown by Fig. 5a, the voltammogram of an aqueous solution of bis( $\alpha$ -iminodipropionato)oxovanadium(IV) is quite similar to that for the iminodiacetate complex. The first cathodic scan shows

peaks at  $-0.95$ ,  $-1.10$ ,  $-1.25$  and  $-1.60$  V. On the second scan the peak at  $-1.25$  V is dominant. As for the earlier complex, the peaks at  $-1.25$  V (reduction) and  $-1.20$  V (oxidation) represent a reversible couple for the complex.

The cyclic voltammogram of 3 mM bis( $\alpha$ -iminodipropionato)oxovanadium(IV) in 0.1 M TEAP/DMSO solution (Fig. 5b) shows additional peaks due to the more positive voltage range accessible in DMSO. The large oxidation wave at 1.10 V may be

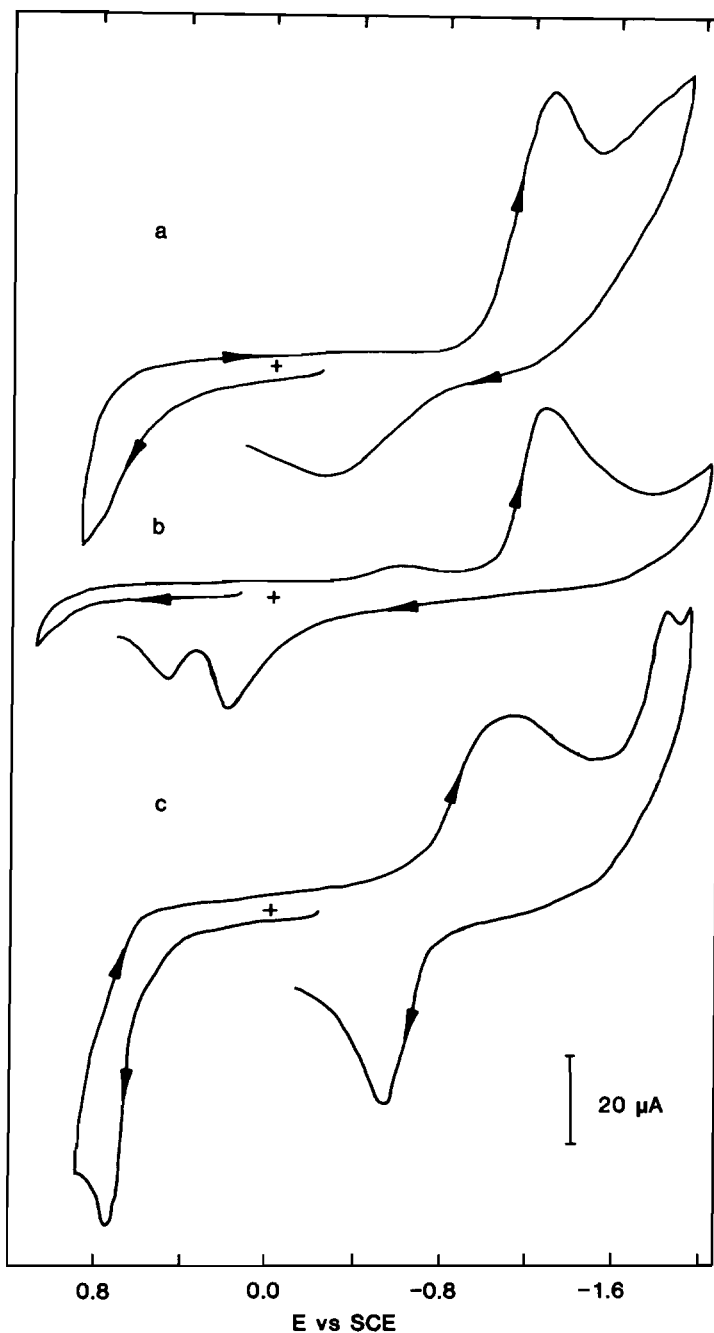


Fig. 6. Cyclic voltammograms in 0.1 M TEAP/DMSO (a) 6 mM  $\beta,\beta$ -iminodipropionic acid. (b) 3 mM  $\text{VO}(\text{ClO}_4)_2$  (c) A 1.3:3 mol ratio mixture of  $\text{VO}(\text{ClO}_4)_2$ :ligand:TEAOH. Scan rate 0.2 V/sec.

due to oxidation of the vanadium(IV) complex to vanadium(V). This process gives rise to the reduction peak at  $-0.70$  V on the second scan. Due to the small size of this peak it appears that the vanadium(V) product is not stable. The oxidation peak at  $0.60$  V has not been identified. The new reduction peak at  $-1.65$  V may be due to free ligand.

Although no complex with  $\beta,\beta$ -iminodipropionic acid could be isolated, a complex was formed in solu-

tion. Figure 6a is a voltammogram of 6 mM  $\beta,\beta$ -iminodipropionic acid in 0.1 M TEAP/DMSO solution. A major reduction peak occurs at  $-1.30$  V and a broad oxidation at  $-0.20$  V. Figure 6b is for a 3 mM solution of  $\text{VO}(\text{ClO}_4)_2$  in DMSO. It reveals no oxidation peaks on an initial anodic scan, but a major reduction peak is near  $-1.30$  V. On a subsequent anodic scan oxidation peaks are observed at  $0.20$  and  $0.50$  V as previously reported [11]. Figure 6c corres-

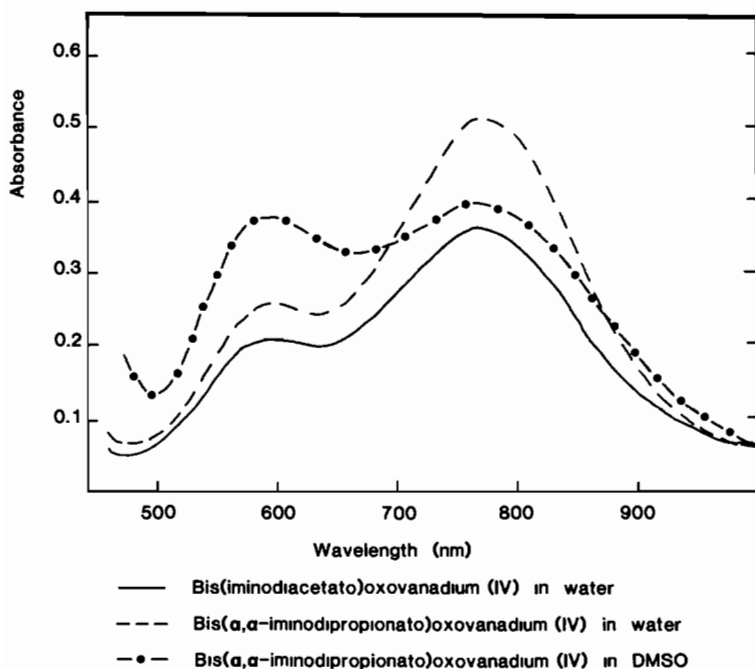


Fig. 7. The visible and near IR spectra of the synthesized complexes in various solvents.

ponds to a 1:3:3 mol ratio mixture of  $\text{VO}(\text{ClO}_4)_2$  to ligand, to TEAOH in DMSO. Of greatest importance is the new oxidation peak at 0.75 V and the broad reduction peak at about  $-1.10$  V. These clearly suggest complex formation and are similar to the peaks observed for the  $\alpha\alpha$ -iminodipropionate complex.

#### Spectroscopy

The visible spectra of the compounds studied are shown in Fig. 7. The spectrum of the iminodiacetate complex was recorded in water, while spectra of the  $\alpha\alpha$ -iminodipropionate complex was recorded both in water and DMSO. The  $\beta\beta$ -iminodipropionate complex prepared in DMSO gave a spectrum similar to that for the  $\alpha\alpha$  isomer. In each spectrum major absorbances occur at 590 and 760 nm. In aqueous solution the 760 nm peak is dominant while the peaks are similar in size in DMSO.

Although no isolated complexes of vanadium with iminodiacid ligands have previously been reported, Napoli and Pontelli [16] and Singh and Tandon [17] have carried out aqueous solution studies of iminodiacetic acid complexes. Both groups focused on probable 1:1 ligand to metal complexes, while only Singh and Tandon even mention a possible 2:1 complex. In light of our isolation of 2:1 compounds, we have carried out several experiments to investigate the possible existence of both 1:1 and 2:1 complexes in solution.

An aqueous solution of bis(iminodiacetato)oxovanadium(IV) has a pH of about 2.5 and exhibits

absorbances at 760 nm and 590 nm. We agree with Napoli and Pontelli (who reached these conditions by titrating vanadyl perchlorate and iminodiacetic acid with NaOH) that the 590 nm peak is due to a complex and that at 760 nm is due to vanadyl ion. Our results also agree in that the 760 nm peak decreases at higher pH and the peak position shifts. Two complexes appear to form, but we disagree with Napoli and Pontelli as to their identity. Those workers suggested the formulas  $\text{VOL}$  and  $\text{VO}(\text{OH})\text{L}^-$  where  $\text{H}_2\text{L} = \text{iminodiacetic acid}$ .

Our synthetic procedures demonstrate that a 1:1 mol ratio of base to ligand is necessary to form  $\text{VOL}_2$  products. To investigate the possibility of an intermediate 1:1 ligand/metal complex we carried out mol ratio studies with  $\alpha\alpha$ -iminodipropionic acid and vanadyl ion in the absence of base. Figure 8 shows spectra for mixtures of  $\alpha\alpha$ -iminodipropionic acid and vanadyl perchlorate with mol ratios of 0:1, 1:1, 2:1, and 3:1 in DMSO. (Without base present complex formation was slow; hence all solutions were allowed to age for two days before spectra were recorded.)

In these spectra, the vanadyl peak is about 820 nm.  $\alpha\alpha$ -Iminodipropionic acid has no absorbance peaks in the visible range. Figure 8, curve 2, shows that two species are present in the 1:1 mol ratio mixture, in addition to vanadyl ion. These species are represented by peaks at 550 and 670 nm. As the ratio of ligand to metal increases the size of the 670 nm peak becomes smaller and disappears, while that at 550 nm becomes dominant. We propose that

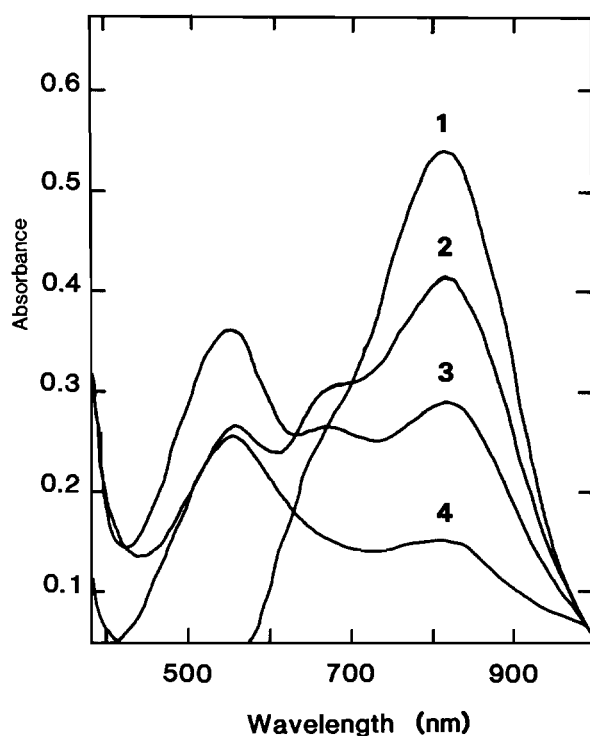


Fig. 8. Visible and near IR spectra of various mol ratios of  $\alpha,\alpha$ -iminodipropionic acid to  $\text{VO}(\text{ClO}_4)_2$  in DMSO in the absence of base. (1) 0:1, (2) 1:1, (3) 2:1, and (4) 3:1.

the 670 nm absorbance is due to a 1:1 complex, VOL, and that the 550 nm absorbance is that of the  $\text{VO}(\text{LH})_2$  complex which we have isolated. Curve 4 for the high ligand to metal ratio mixture compares well with Fig. 7.

The presence of the intermediate 1:1 complex was also demonstrated by a mol ratio study in which the ligand concentration was held constant while the vanadyl ion concentration was increased. The results are shown in Fig. 9. Curves 1–5 represent ligand:metal mol ratios of 1:0.29, 1:0.43, 1:0.57, 1:0.71, and 1:1, respectively. Curves 1 and 2 indicate that when there is an excess of ligand the 2:1 complex,  $\text{VO}(\text{LH})_2$ , is dominant (absorbance at 550 nm). At lower ratios of ligand to metal an additional species is important, VOL (shoulder at 670 nm). Clearly, uncomplexed  $\text{VO}^{2+}$  exists in all cases. These data agree with that of Fig. 8. Qualitatively, it should also be noted that in both sets of experiments, when the 670 nm peak is observed the solution color changes from blue to magenta.

As a final comparison, the isolated product, bis( $\alpha$ -iminodipropionato)oxovanadium(IV), was dissolved in DMSO with additional  $\text{VO}(\text{ClO}_4)_2$  present. The spectrum of the initial solution was identical to that of Fig. 9, curve 1. After four days the solution turned a magenta color and the spectrum was similar to that of Fig. 9, curve 3.

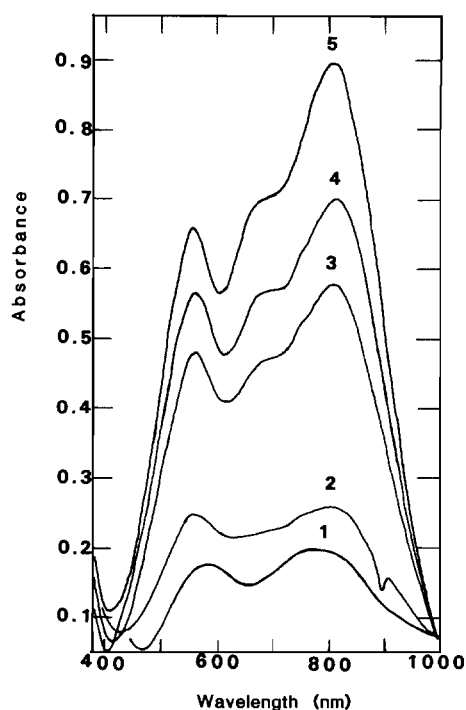


Fig. 9. Visible and near IR spectra of various mol ratios of  $\alpha,\alpha$ -iminodipropionic acid to  $\text{VO}(\text{ClO}_4)_2$  in DMSO in the absence of base (1) 1:0.29, (2) 1:0.43, (3) 1:0.57, (4) 1:0.71, and (5) 1:1.

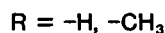
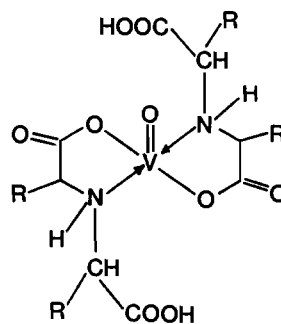


Fig. 10. Proposed structure of bis(iminodiacetato)oxovanadium(IV) and bis( $\alpha,\alpha$ -iminodipropionato)oxovanadium(IV).

## Conclusions

We have reported here the first isolation of bis(iminodiacetato)oxovanadium(IV) and bis( $\alpha$ -iminodipropionato)oxovanadium(IV). Bis( $\beta$ -iminodipropionato)oxovanadium(IV) was studied in solution, but could not be isolated as a pure product.

In these complexes the ligands (I, II, and III in Fig. 2) are bidentate, singly charged anions, bonded to



vanadium through oxygen and nitrogen atoms. We propose the structure shown in Fig. 10. Several pieces of data show that only one carboxylate group is bonded. 1. The isolated compounds with two ligands require that the anions must be singly charged. 2. The IR spectra show two types of C=O stretches. 3. The pH titrations indicate two acidic protons per molecule.

It should be noted that this structure is in contrast to those for complexes of other metals with these ligands. Typically, for  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ , and  $\text{Sn}^{2+}$  1:1 complexes are formed with such ligands as tridentate donors [18–20]. In these complexes the ligands bond through two carboxylate oxygens and the nitrogen. However, it was also suggested by Chaberek and Martel [21] that in the presence of excess ligand, copper in solution equilibrates forming both 1:1 and 2:1 ligand to metal complexes. The 2:1 complex is thought to bond through nitrogen and one oxygen.

In the structure in Fig. 10 it can be seen that both the iminodiacetate and  $\alpha\alpha$ -iminodipropionate ligands form five membered rings with the vanadium atom. In contrast, the complex with  $\beta\beta$ -iminodipropionate yields a six membered ring. This larger ring size may account for the instability of this complex.

Our results also suggest the presence of 1:1 complexes in solution at low mol ratios of ligand to metal. These results agree with those of Napoli and Pontelli [16] and Singh and Tandon [17] but we doubt that a  $\text{VO}(\text{OH})\text{L}^-$  complex forms, as suggested by the first authors. Rather, our data suggest that the second equivalent of base is required to deprotonate a second ligand, resulting in a  $\text{VO}(\text{LH})_2$  complex as we have isolated. Singh and Tandon do propose a 2:1 complex similar to ours, but with the non-bonded carboxylate groups deprotonated, hence  $\text{VOL}_2^{2-}$ .

Only a preliminary interpretation can be given of the electrochemical results. The multiple overlapping reduction peaks suggest various species in solution. This agrees with the demonstrated presence of 1:1 and 2:1 complexes in addition to  $\text{VO}^{2+}$ . The couple near  $-1.2$  V may represent a reversible reduction of the 2:1 complexes. The studies in DMSO clearly show that no stable vanadium(V) complexes are formed upon oxidation. Thus, only the (IV) and (III) oxidation states are likely to be important in biological systems.

#### Comparison to Amavadine

Kneifel and Bayer [5, 6] reported elemental analysis and spectral data for the natural product, Amavadine, but were unable to determine its structure directly. Therefore, they synthesized an analogue (Fig. 1) for comparison. They concluded that the two were the same, except for optical configuration. We have tried to prepare the ligand N-

hydroxy- $\alpha,\alpha$ -iminodipropionic acid, from their outline (hydroxylamine HCl and  $\alpha$ -bromopropionic acid at pH 10) but have been unsuccessful. Therefore, we have chosen to study model complexes, while our efforts on the synthesis of Amavadine continue.

There are several significant similarities between our compounds (Fig. 10) and Amavadine (Fig. 1). Both are blue compounds which decompose without a melting point. Our compounds have C=O stretching frequencies of  $1617\text{ cm}^{-1}$  for the coordinated carboxylate, while Kneifel and Bayer report the C=O stretch at  $1600\text{--}1650\text{ cm}^{-1}$ . (A second band for C=O was not mentioned). The V=O stretch was in the typical range for both compounds. The three important absorbances in the visible spectra of our complexes were at 590, 670, and 760–820 nm. Kneifel and Bayer report absorbances at 565, 715, and 775 nm which could be due to the same transitions. Those authors also reported that titration with NaOH yielded two equivalence points, in agreement with our work. Finally, the data from both studies suggest the structures shown, where each ligand is bidentate, carries a single negative charge, and is bound through one oxygen and one nitrogen atom.

We hope to report in the future on the synthesis of N-hydroxy- $\alpha,\alpha$ -iminodipropionic acid and Amavadine, and a detailed study of their electrochemistry.

#### Acknowledgements

This work was supported by the Research Corp. and by Sigma Xi, The Scientific Research Society.

#### References

- 1 L. L. Hopkins, Jr. and H. E. Mohr, in W. Mertz and W. E. Cornatzer, (eds.), 'Newer Trace Elements in Nutrition', Marcel Dekker, New York, 1971, pp. 195–213.
- 2 F. H. Nielsen, in A. E. Martell (ed.), 'Inorganic Chemistry in Biology and Medicine', American Chemical Society, Washington, 1980, chapter 2
- 3 I. G. Macara, *Trends in Biochem Sci*, April 1980, p. 92.
- 4 Early reports of a vanadium chromogen isolated from the blood of certain tunicates were apparently dealing with an artifact of the isolation procedure. In tunicates, vanadium is now believed to exist as a labile vanadium(III) aquo complex. R. M. K. Carlson, *Proc Nat Acad. Sci. USA*, 72, 2217 (1975).
- 5 E. Bayer and H. Kneifel, *Z. Naturforsch.*, 27B, 207 (1971)
- 6 H. Kneifel and E. Bayer, *Angew Chem Int Ed.*, 12, 508 (1973)
- 7 T. L. Riechel and D. T. Sawyer, *Inorg Chem.*, 14, 1869 (1975).
- 8 M. Michlmayr and J. Gutmann, *J. Inorg. Chem. Acta*, 1, 471 (1967).
- 9 J. V. Dubsy, *Berichte*, 49, 1045 (1916)
- 10 J. H. Ford, *J. Am Chem Soc.*, 67, 876 (1945).

- 11 B. J. Gallagher and T. L. Riechel, *Inorg Chim. Acta*, **66**, 73 (1982).
- 12 C. A. McAuliffe, J V Quagliano and L M Vallarino, *Inorg. Chem.*, **5**, 1996 (1968).
- 13 H Shindo and T L Brown, *J Am Chem Soc*, **87**, 1904 (1965)
- 14 S. Kirshner, *J Am. Chem Soc*, **78**, 2372 (1956)
- 15 J. Selbin, *Coord Chem. Rev.*, **1**, 293 (1966)
- 16 A Napoli and L. Pontelli, *Gazz. Chim Ital*, **103**, 1219 (1973)
- 17 S P. Singh and J P Tandon, *J Prakt Chem.*, **315**, 23 (1973)
- 18 L Korecz, A A. Saghier, K Burger, A. Tzschach and K Jurkschat, *Inorg Chim Acta*, **58**, 243 (1982)
- 19 R V Snyder, R J. Angelici and R B. Meck, *J Am Chem. Soc*, **94**, 2660 (1972).
- 20 R V. Snyder and R J Angelici, *Inorg. Chem*, **13**, 14 (1974)
- 21 S Chaberek, Jr. and A E Martell, *J Am Chem Soc*, **74**, 5052 (1952).