Vanadium in Biology and Medicine

CASE STUDY 4

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Overview

- Vanadium Chemistry
- Peroxidases
- Insulin Activity
- Vanadium as a mimetic

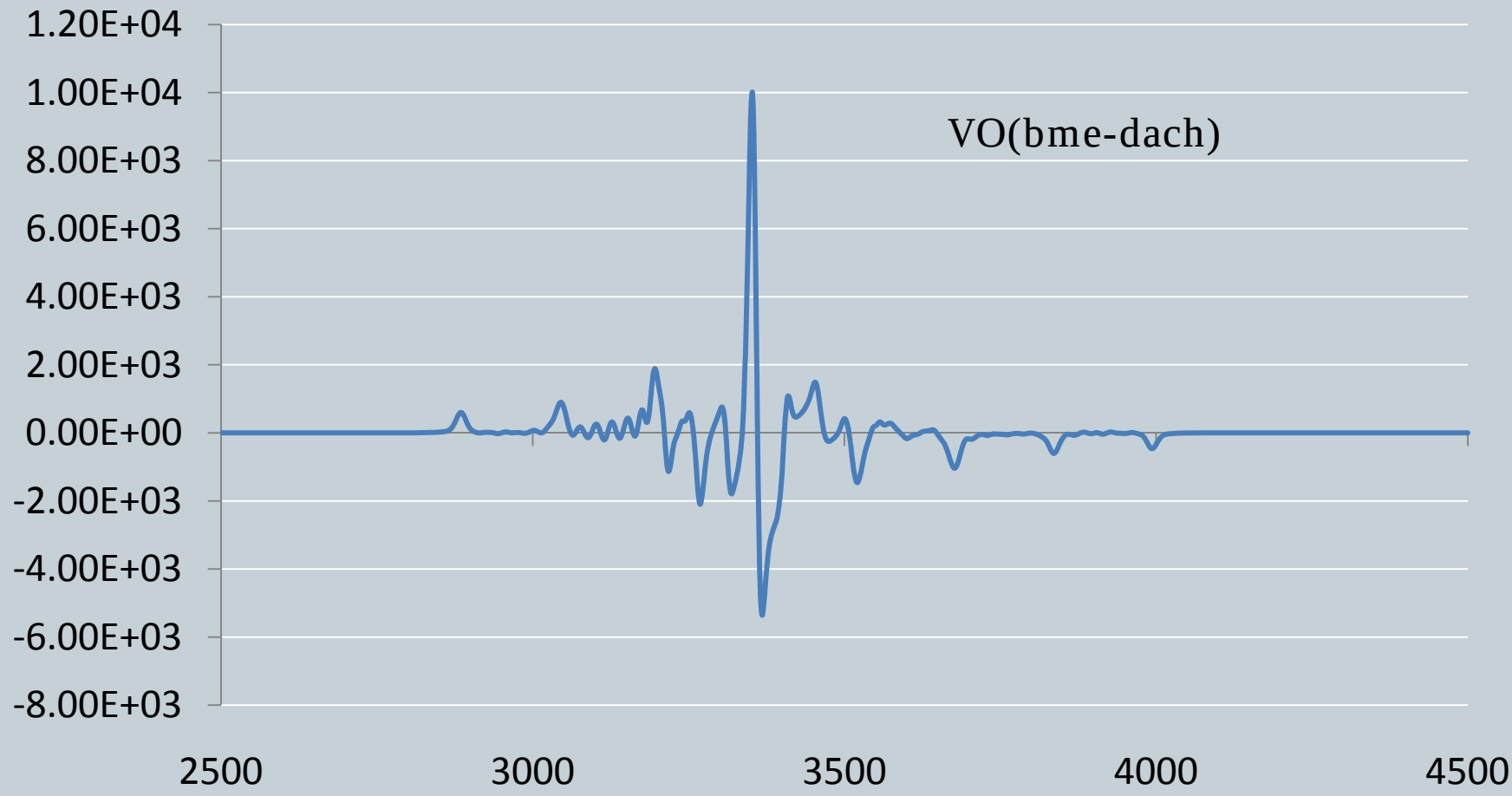
Vanadium

- Oxidation States from the -1 to the +5 but the major ones to us are the +3, +4, +5
- In higher oxidation states has an affinity for nitrogen and oxygen donors which can be explained by HSAB
- Usually has vanadyl in synthetic drugs $(V{=}O)^{++}$
- Solutions are a green color
- Essentiality determined in 1973 through studies of rats but still uncertain in humans

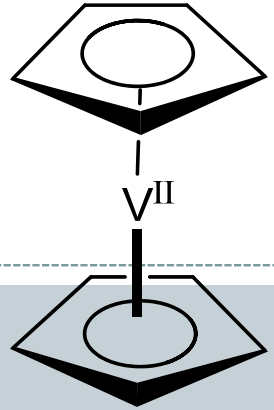
Vanadium Continued

- Paramagnetic
- d^1 configuration
- Nuclear spin of 7/2

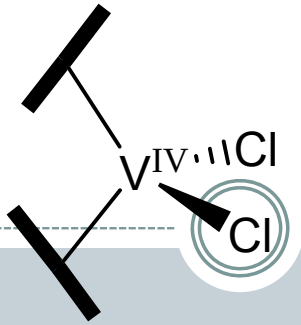
EPR


1.20E+04
1.00E+04
8.00E+03
6.00E+03
4.00E+03
2.00E+03
0.00E+00
-2.00E+03
-4.00E+03
-6.00E+03
-8.00E+03
2500
3000
3500
4000
4500
VO(bme-dach)

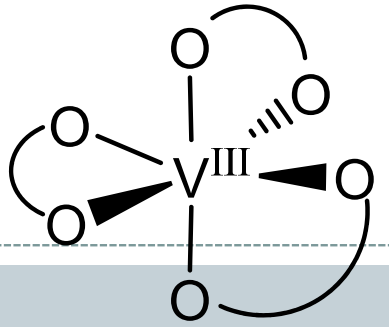
Catalog Sources of Vanadium



Vanadocene



Biscyclopentadienyl
Vanadium(IV) dichloride



$V^{III}(acac)_3$
acac = acetylacetonate

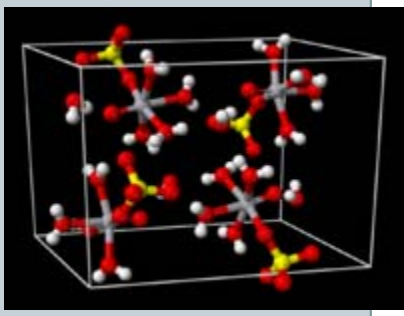
$V^{III}X_3$
Vanadium halides

$[V^{IV}{=}O][SO_4]^{2-}$ x $(H_2O)_4$
Vanadyl sulfate

$V^{V}OCl_3$
Vanadium(V) trichloride oxide

Vanadyl Ion

- The vanadyl ion is one of the most stable diatomic ions
- Can be explained by HSAB
- Blue solid and most common source of vanadium in the laboratory
- Oxidation state of +4



- Present in all of the haloperoxidases and most synthetic vanadium drugs

Haloperoxidases

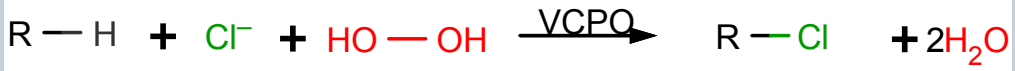
- Enzymes that catalyze the oxidation of a halide by hydrogen peroxide
- Chloro, Bromo, Iodo peroxidases
- Three types: heme group, vanadium, “metal free”
- First time vanadium was seen as a cofactor

Cofactor

- Commonly referred to as “helper molecules”
- Bound to the outside of a protein
- Required for enzyme activity

Haloperoxidases Continued

- See the conversion of X^- to X^+ followed by halogenation of the organic molecule or formation of singlet oxygen



- Vanadium is in the +5 oxidation state

- Big deal in industry because of mild conditions

Haloperoxidase in Nature

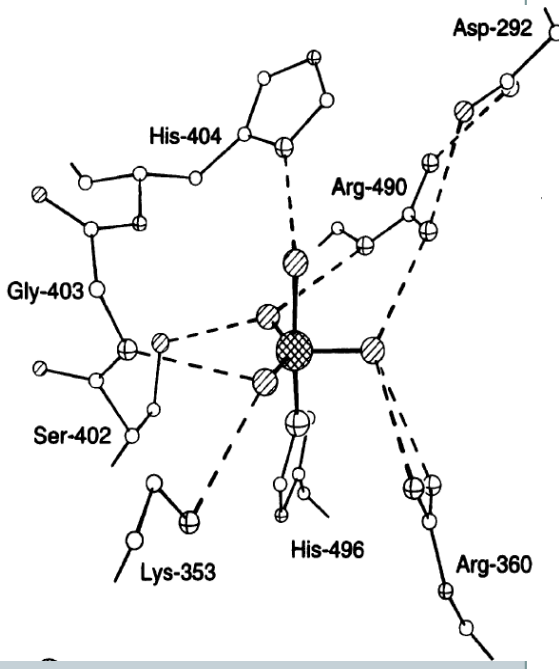
- Found in humans in the thyroid as thyroidperoxidase and saliva as lactoperoxidase
- Found in white blood cells as myeloperoxidase and eosinophilperoxidase
- Also found in marine algae
- Sea urchin eggs

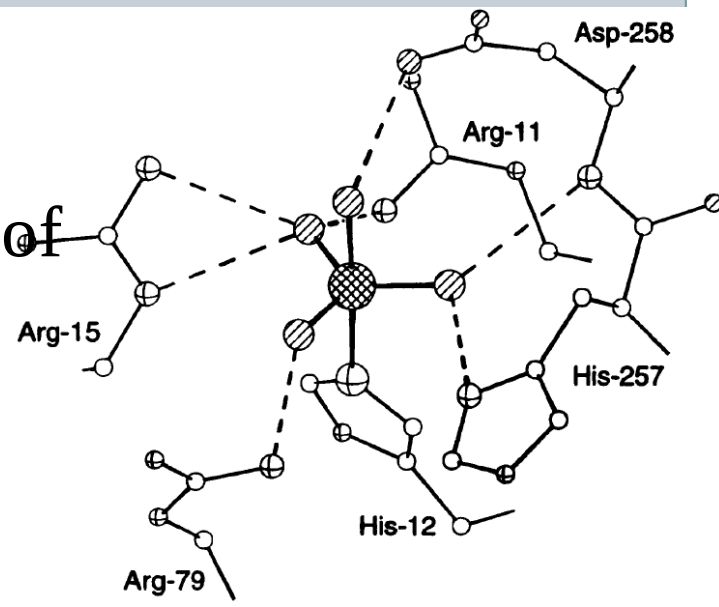
Structure of Haloperoxidase

- Trigonal Bipyramidal
- Bound to one histidine
- Bound to at least 3 oxygen atoms and in most cases 4 although sometimes an azide
- Structure of lactoperoxidase

Binding to Protein

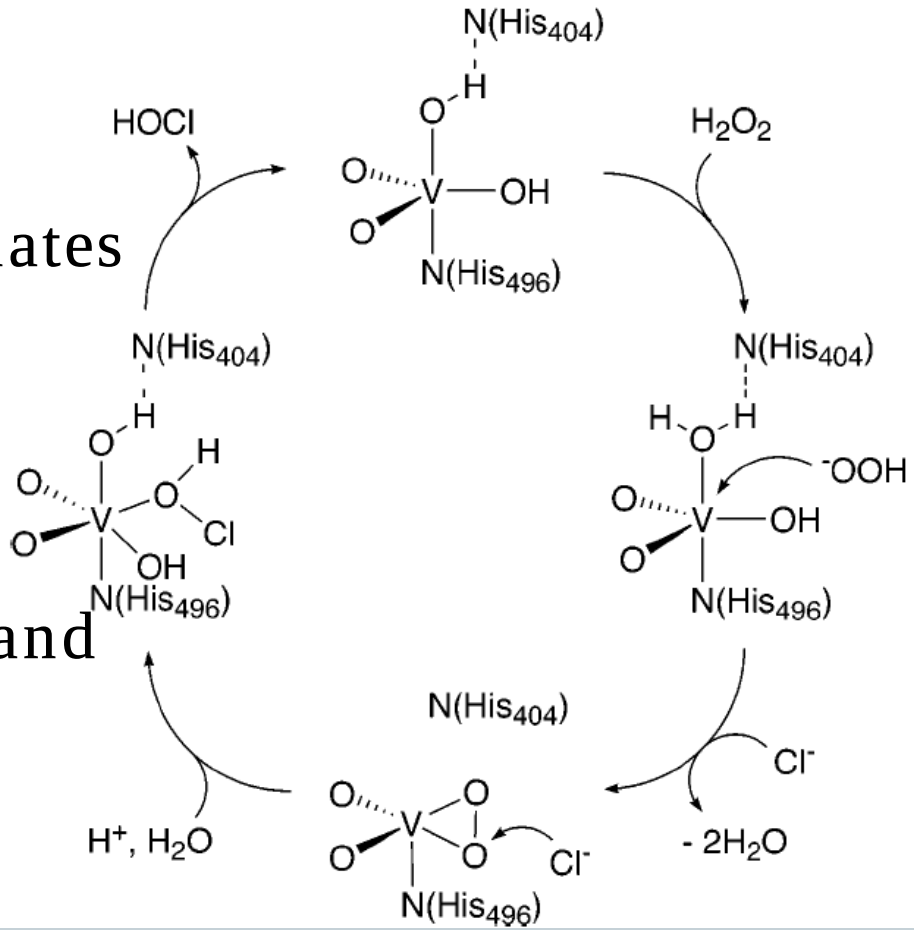
- Hydrogen Bonding to the protein
- Keeps the vanadium in place
- Easy hydrogen bonding to oxygen
- Structure very close to phosphatases (Top is VCPO)
- Idea is that vanadium inhibited phosphatases act as haloperoxidases in the presence of hydrogen peroxide





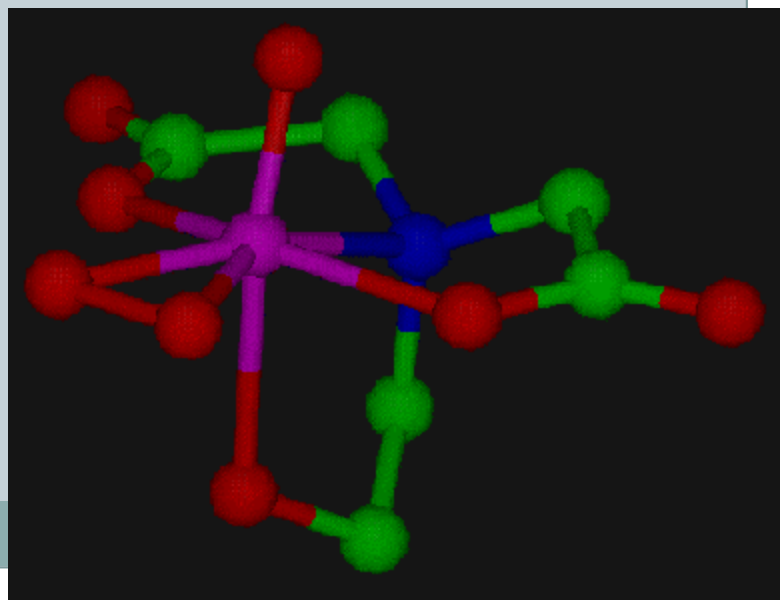
Proposed Mechanism

- Center is two histidines
- Hydrogen peroxide protonates the oxygen and adds to vanadium
- Loss of 2 waters with the chloride opening the ring
- Water adds with a proton and the HOCl leaves
- Halide doesn't add to vanadium
- Can produce singlet oxygen



Synthetic Analogues

- Act as functional models for vanadium peroxidases
- $[VO(O_2)Hheida]^-$
- In acetonitrile, works well to catalyze the addition of the halide
- NO_6

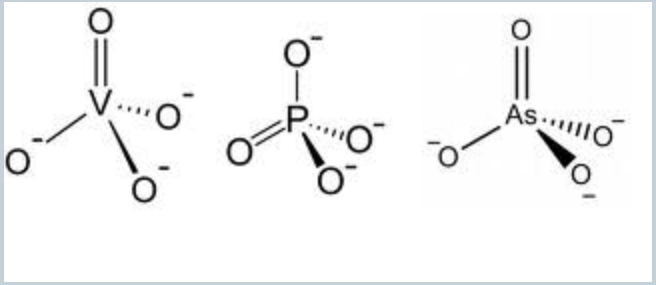


Wrapping up Peroxidases

- Potentially used to oxidize sulfides to sulfoxides
- Peroxidase from bacteria and algae was used to test this idea
- Assuming that this halogenation process is required in the body then this is the first time vanadium is established as a required metal

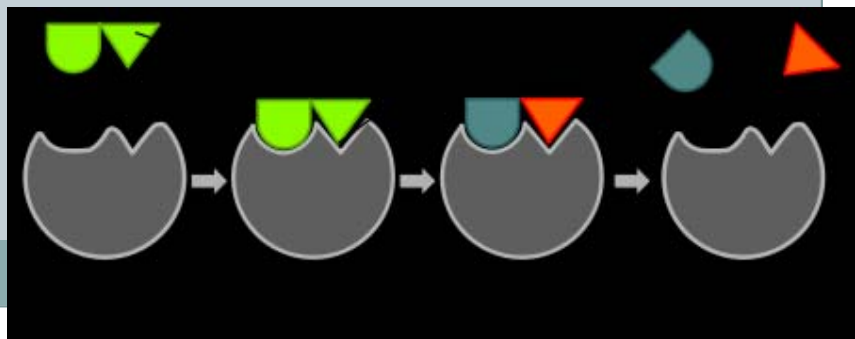
Inhibition of Phosphorylation

- Phosphatases catalyze the hydrolysis of phosphate ester bonds. Removes a phosphate group
- Likely to be important to the insulin like activity of vanadium
- Phosphatases are inhibited by oxometalate anions such as vanadate, arsenate, tungstate
- Transition State Analogue



Transition State Analogues

- Compounds with chemical structures similar to the transition state of the substrate
- Inhibit the active site of the enzyme
- As seen below the substrate fits perfectly. Vanadyl is able to substitute for phosphate in the perfect fit. Might not be able to leave after being modified



Vanadium as Insulin Mimetic

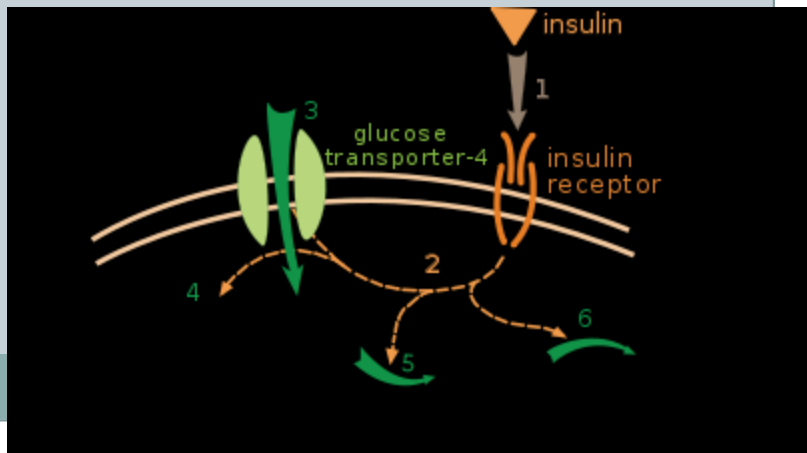
- Known since the 1980's
- Diabetes patients have abnormal glucose and lipid metabolism
- Normally treat with increased insulin levels
- Vanadium compounds alleviate the symptoms of diabetes and enhance the action of insulin

Diabetes/Insulin action

- Type I- Doesn't produce enough insulin
- Type II- Insulin resistance
- Signaling action of insulin in the body is still not known completely
- Vanadium compounds look at type II diabetes

Insulin Activity

- Secreted by the pancreas after uptake of food
- Increased insulin promotes uptake of glucose by the liver and gut as well as peripheral tissue
- This results in energy production



Signaling

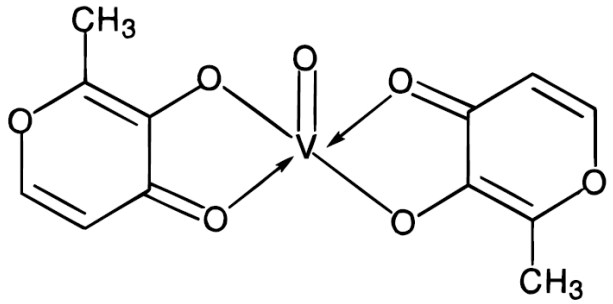
- Insulin binds to the cell membrane at the insulin receptor which promotes uptake
- This sets off a series of phosphorylation steps which can be substituted by, and are very sensitive to, vanadium
- Led to increased insulin levels and to obesity resistance
- Resistance to insulin by the receptor leads to type II diabetes

Compounds/Requirments

- Oxidation state not as critical although most are in the +3, +4, +5 due to standard conditions in the body
- Potency depends on the ligands attached
- Ligands must be thermodynamically and hydrolytically stable in water
- Administered orally (water soluble, neutral charge)
- No toxic biological products
- Must be able to cross lipid interfaces in cells

BMOV

- Bis(maltolato)oxovanadium(IV)
- Oxygen-rich ligands tend to be water soluble
- Square pyramidal complex
- Dosage of 0.4 mmol/kg per day
- Passed first phase of clinical trials and given in drinking water
- 50% glucose lowering



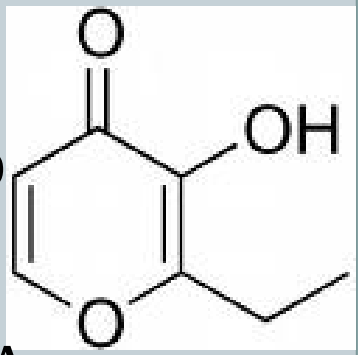
BMOV, $[VO(ma)_2]$

Clinical Trial Phases

- Phase 0- Too low to do any good. Goal is it see if it acts the way it should in the body
- Phase I- (20-100 people) Assess safety and tolerability under a physicians sight to see side effects
- Phase II- (more people) Goal is to see if the drug does what it says it does (failure occurs here)
- Phase III- (300-3000 people) Random people
- Phase IV- On going investigation to make sure it works

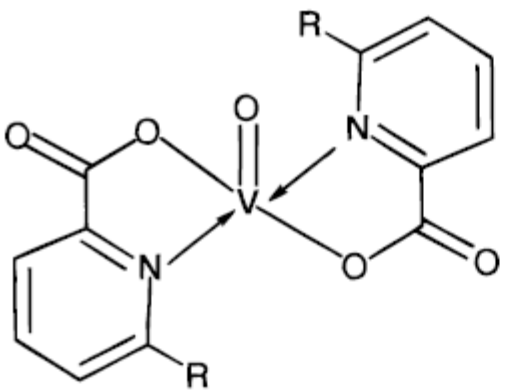
Synthesis

- Very simple and in high yield
- Vanadyl sulfate is added to two portions of Maltol (bottom right)
- A base is used to deprotonate the OH group
- Maltol is approved as a food additive in USA

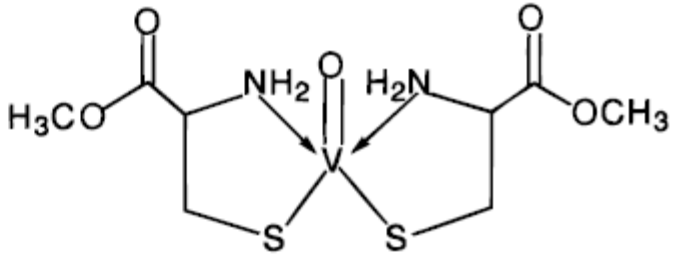


Other Compounds

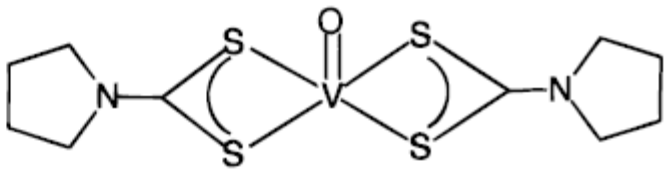
- Other vanadium compounds looking at testing but have been inferior to BMOV



VPA, R = H
VO-MPA, R = CH_3



Vanadyl bis(cysteine methyl ester)



V-P

Toxicity

- Failure to gain weight
- Gastric irritation due to poor absorption
- Green tongue
- No evidence to show that increased storage in bone is harmful
- Deprivation increase thyroid weight