

## 1.6: Transport of Zinc, Copper, Vanadium, Chromium, Molybdenum, and Cobalt

As described in an earlier section, transport problems posed by the six elements listed in the heading are somewhat simpler (with the exception of chromium) than those for iron. One very interesting recent development has been the characterization of sequestering agents produced by plants which complex a number of metal ions, not just ferric ions. A key compound, now well-characterized, is mugenic acid (Figure 1.17).<sup>45</sup> The structural and chemical similarities of mugenic acid to ethylenediaminetetraacetic acid (EDTA) have been noted. Like EDTA, mugenic acid forms an extremely strong complex with ferric ion, but also forms quite strong complexes with copper, zinc, and other transition-metal ions. The structure of the cobalt complex (almost certainly essentially identical with that of the iron complex) is shown in Figure 1.18. Like the siderophores produced by microorganisms, the coordination environment accommodated by mugenic acid is essentially octahedral. Although the coordination properties of this ligand are well laid out, and it has been shown that divalent metal cations, such as copper, competitively inhibit iron uptake by this ligand, the detailed process of metal-ion delivery by mugenic acid and related compounds has not been elucidated.

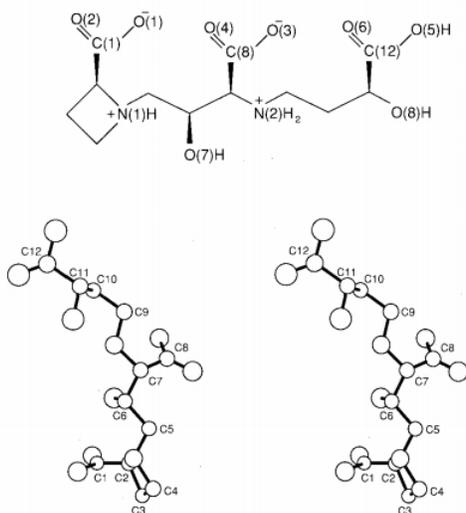


Figure 1.17 - Structure and a stereo view of mugenic acid. See Reference 42.

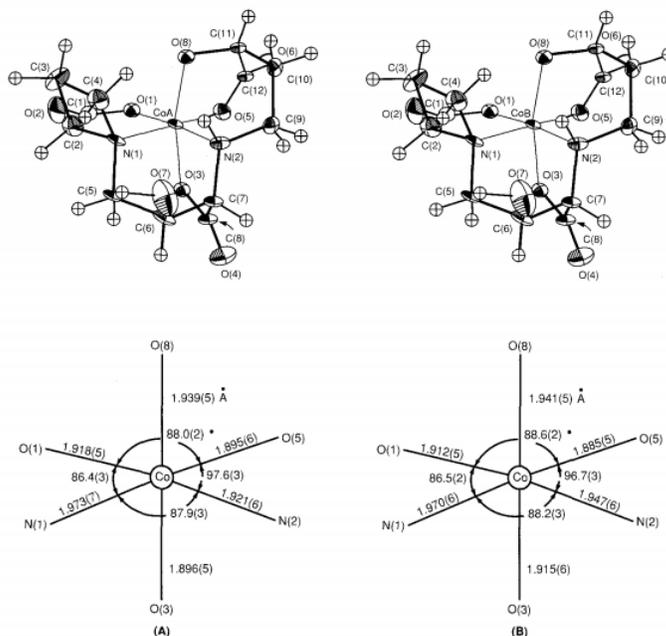


Figure 1.18 - Molecular structures of the complexes (molecules A and B) and coordination about the cobalt ion in molecules A and B of the mugenic acid-Co(III) complex. Bond lengths in Å; angles in degrees. See Reference 42.

As noted in an earlier section, the biochemistry of vanadium potentially involves four oxidation states that are relatively stable in aqueous solution. These are  $V^{2+}$ ,  $V^{3+}$ ,  $VO^{2+}$ , and  $VO_2^{+}$  (the oxidation states 2, 3, 4, and 5, respectively). Since even without added sequestering agents,  $V^{2+}$  slowly reduces water to hydrogen gas, it presumably has no biological significance. Examples of the remaining three oxidation states of vanadium have all been reported in various living systems. One of the most extensively investigated examples of transition-metal-ion accumulation in living organisms is the concentration of vanadium in sea squirts (tunicates), which is reported to be variable; many species have vanadium levels that are not exceptionally high. Others such as *Ascidia nigra* show exceptionally high vanadium concentrations.<sup>46</sup>

In addition to showing a remarkable concentration of a relatively exotic transition-metal ion, tunicates are a good laboratory model for uptake experiments, since they are relatively simple organisms. They possess a circulation system with a one-chambered heart, and a digestive system that is essentially a pump and an inlet and outlet valve connected by a digestive tract. The organism can absorb dissolved vanadium directly from sea water as it passes through the animal. The influx of vanadate into the blood cells of *A. nigra* has been studied by means of radioisotopes. The corresponding influx of phosphate, sulfate, and chromate (and the inhibition of vanadate uptake by these structurally similar oxoanions) has been measured. In the absence of inhibitors, the influx of vanadate is relatively rapid (a half-life on the order of a minute near 0 °C) and the uptake process shows saturation behavior as the vanadate concentration is increased. The uptake process (in contrast to iron delivery in microorganisms, for example, and to many other uptake processes in microorganisms or higher animals) is *not* energy-dependent. Neither inhibitors of glycolysis nor decouplers of respiration-dependent energy processes show any significant effect on the rate of vanadate influx.

Phosphate, which is also readily taken up by the cells, is an inhibitor of vanadate influx. Neither sulfate nor chromate is taken up significantly, nor do they act as significant inhibitors for the vanadate uptake. Agents that inhibit transport of anions, in contrast, were found to inhibit uptake of vanadate into the organism. These results have led to the model proposed in Figure 1.19:

1. vanadate enters the cell through anionic channels; this process eliminates positively charged metal ion or metal-ion complexes present in sea water;
2. vanadate is reduced to vanadium(III); since the product is a cation, and so cannot be transported through the anionic channels by which vanadate entered the cell, the vanadium(III) is trapped inside the cell-the net result is an accumulation of vanadium. [It has been proposed that the tunichrome could act either as a reducing agent (as the complex) or (as the ligand) to stabilize the general vanadium(III); however, this seems inconsistent with its electrochemical properties (see below).]

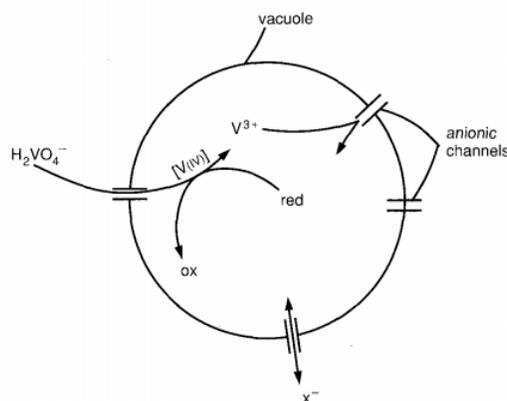


Figure 1.19 - Diagram of a vanadium accumulation mechanism. Vanadium enters the vacuole within the vanadocyte as mononegative  $H_2VO_4^-$ , although it may be possible for the dinegative anion,  $HVO_4^{2-}$ , to enter this channel as well ( $X^-$  stands for any negative ion such as  $Cl^-$ ,  $H_2PO_4^-$ , etc., that may exchange across the membrane through the anionic channel). Reduction to  $V^{3+}$  takes place in two steps, via a  $V(IV)$  intermediate. The resulting cations may be trapped as tightly bound complexes, or as free ions that the anionic channel will not accept for transport. The nature of the reducing species is unknown.

Synthetic models of tunichrome b-1 (Figure 1.20) have been prepared. Tunichrome is a derivative of pyrogallol whose structure precludes the formation of an octahedral complex of vanadium as a simple 1:1 metal:ligand complex. The close analogue, described as 3,4,5-TREN $PAMH_9$ , also cannot form a simple octahedral 1:1 complex. In contrast, the synthetic ligands TREN $CAM$  and 2,3,4-TREN $PAM$  can form pseudo-octahedral complexes. The structure of the vanadium TREN $CAM$  complex shows that it is indeed a simple pseudo-octahedral tris-catechol complex.<sup>47</sup> The electrochemical behavior of these complexes is similar, with vanadium(IV/III) potentials of about -0.5 to -0.6 volts versus NHE. These results indicate that tunichrome b-1 complexes of vanadium(IV/III) would show similar differences in their redox couples at high pH. At neutral pH, in the presence of excess pyrogallol groups, vanadium(IV) can be expected to form the intensely colored tris-catechol species. However, comparison of the

EPR properties reported for vanadium-tunichrome preparations with model vanadium(IV)-complexes would indicate predominantly bis(catechol) vanadyl coordination. In any case, the vanadium(III) complexes must remain very highly reducing. It has been pointed out that the standard potential of pyrogallol is 0.79 V and decreases 60 mV per pH unit (up to about pH 9), so that at pH 7 the potential is about 0.4 V. The potentials of the vanadium couples for the tunichrome analogs are about -0.4 V. It has been concluded, therefore, that tunichrome or similar ligands cannot reduce the vanadium(IV) complex; so the highly reducing vanadium(III) complex of tunichrome must be generated in some other way.<sup>47</sup>

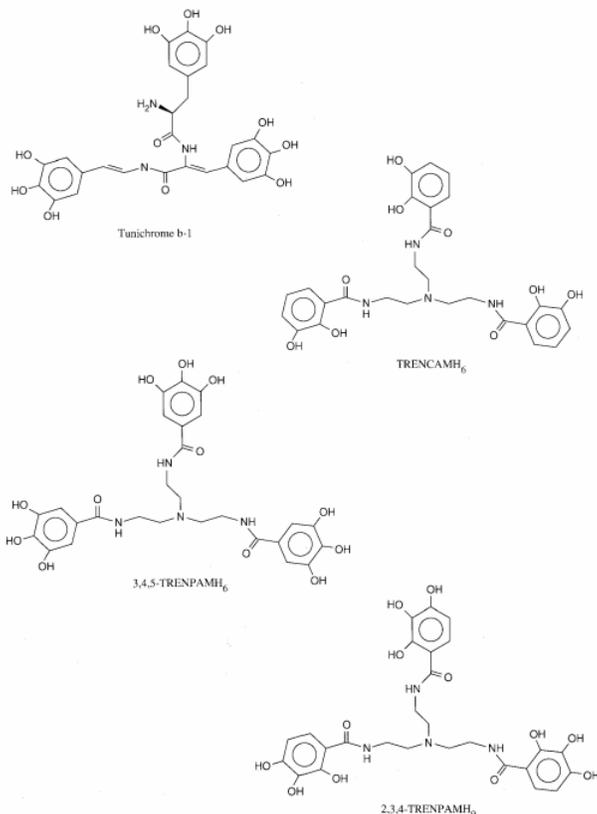


Figure 1.20 - Structures of tunichrome b-1 and synthetic analogues.<sup>43</sup>

Although a detailed presentation of examples of the known transport properties of essential transition-metal ions into various biological systems could be the subject of a large book, the examples that we have given show how the underlying inorganic chemistry of the elements is used in the biological transport systems that are specific for them. The regulation of metal-ion concentrations, including their specific concentration when necessary from relatively low concentrations of surrounding solution, is probably one of the first biochemical problems that was solved in the course of the evolution of life.

Iron is transported in forms in which it is tightly complexed to small chelators called siderophores (microorganisms) or to proteins called transferrins (animals) or to citrate or mugenic acid (plants). The problem of how the iron is released in a controlled fashion is largely unresolved. The process of mineral formation, called biomineralization, is a subject of active investigation. Vanadium and molybdenum are transported as stable anions. Zinc and copper appear to be transported loosely associated with peptides or proteins (plants) and possibly mugenic acid in plants. Much remains to be learned about the biological transport of nonferrous metal ions.

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