

Tungsten in Life and Medicine

One of the more unusual papers given at an ITIA conference was “Tungsten in Life and Medicine” by Dr Philip Mitchell (*pictured below*), Emeritus Reader of Chemistry, University of Reading, UK. Described as a brilliant presentation by several delegates, it was such an absorbing review – for scientists and non-scientists alike – of the part played by tungsten in the origins of life and some exciting prospects for tungsten’s future in medical applications that we are re-printing it here for a wider audience.

A hydrothermal vent on the ocean floor. Hydrothermal vents (black smokers) support a variety of archaea. The discovery of the archaea in extreme environments suggests that life evolved under hellish conditions. See page 4 for the story.

Credit: P. Rona, US National Oceanic and Atmospheric Administration (NOAA), Office of Ocean and Atmospheric Research (OAR)/National Undersea Research Program (NURP) 2010

That tungsten *does* have a role in biology may be surprising to those who think of tungsten as an exotic heavy metal known for its uses in alloy steels, in electric light filaments and as the source in tungsten carbide of one of the hardest materials known. In this article my aims are

- to describe and understand tungsten in biology;
- to understand how tungsten in biology is related to tungsten chemistry;
- to compare and contrast tungsten and molybdenum in biology and in chemistry;
- to describe some applications of tungsten in medicine.



We shall see that tungsten was essential for the development of life on earth; that there is a biological requirement for tungsten; that there is continuing interest in medical applications of tungsten compounds.

Author’s note: I use tungsten as a generic term for tungsten and its compounds. However, mostly we are actually referring to the tungstate anion. Just as when we write about sulfate we refer to sulfate and not sulfur so it is generally appropriate to refer to tungstate rather than tungsten although this is not the general practice.

Figure.1: Yellowstone National Park



TUNGSTEN-DEPENDENT BACTERIA

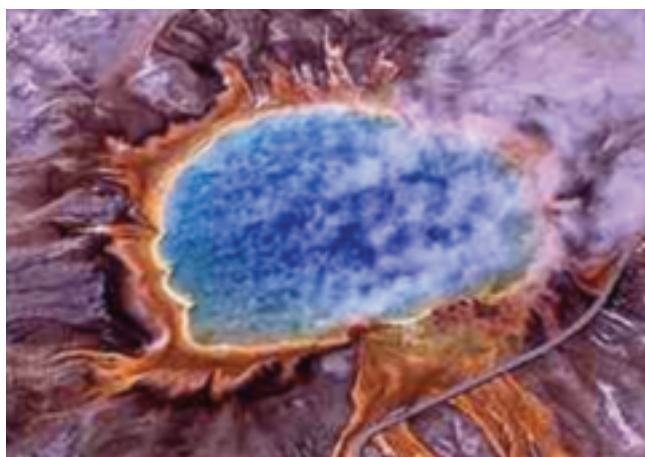
We can start our *tungsten in life* story in various places. One is in the Yellowstone National Park in Wyoming in the United States (**Figure 1**). There we find the 'Grand Prismatic Spring' which is the largest hot spring in the United States and is noted for its bright and varied colours (**Figure 2**). The colours are due to primitive single-cell micro organisms – *archaea* and *bacteria*. They are:

- *anaerobic*: not requiring oxygen – and poisoned by oxygen;
- *thermophiles* or *hyperthermophiles*: organisms that thrive at temperatures which may approach 100°C
- *ancient* in the evolutionary timescale: 3.8 billion years old;
- *tungsten-dependent*; to grow and thrive they need tungstate.

They are found in hydrothermal vents in the deep ocean, near volcanoes, and in stagnant ponds. An example is the bacterium

Figure 2: Grand Prismatic Spring, Yellowstone National Park.

The colours are due to primitive single-cell microorganisms – *archaea* and *bacteria*. http://en.wikipedia.org/wiki/Grand_Prismatic_Spring.



clostridium thermoaceticum (**Figure 3**) which is found in under-sea thermal vents and at the bottom of stagnant ponds. It is an anaerobe and thermophile, stable above 64°C and is *tungsten-dependent*. The chemical reactions associated with these primitive micro-organisms involve carbon dioxide reacting, for example, with hydrogen to give formic acid or acetic acid (**Figure 4**). We may consider such reactions, which give carbon compounds with carbon-carbon bonds, to have been the first life-originating reactions, producing molecules which are the pre-cursors of the molecules of life. These reactions need tungsten.

Kletzin, A. and Adams, M. W. W. Tungsten in biological systems. *FEMS Microbiology Reviews*, 1996, 18, 5–63.

Stiefel, E.I. The biogeochemistry of molybdenum and tungsten in Sigel, A. and Sigel, H. (eds.) *Metal Ions in Biological Systems*, Vol. 39, 2002, Molybdenum and Tungsten: Their Roles in Biological Processes, Marcel Dekker Inc. New York, p.1.

Pau, R.N. and Lawson D.M. Transport, homeostasis, regulation, and binding of molybdate and tungstate to proteins in A. Sigel and H. Sigel (eds.) *Metal Ions in Biological Systems*, Marcel Dekker, Vol. 39, 2002, p. 43.

Voholt, J.A. and Thauer, R.K. Molybdenum and tungsten enzymes in C1 metabolism in A. Sigel and H. Sigel (eds.) *Metal Ions in Biological Systems*, Marcel Dekker, Vol. 39, 2002, p. 571.

Beyers, L.E. Hagedoorn, P.-L. Hagen W.R. The bioinorganic chemistry of tungsten. *Coordination Chemistry Reviews*, 2009, 253,269–290.

Johnson, M. K., Rees, D. C. and Adams, M. W. W. Tungstoenzymes. *Chem. Rev.* 1996, 96, 2817-2839, Lvov, N. P., Nosikov, A. N. and Antipov, A. N. Tungsten-containing enzymes *Biochemistry (Moscow)*, 2002, 67, 196-200.

Sugimoto, H. and Tsukube, H. Chemical analogues relevant to molybdenum and tungsten enzyme reaction centres toward structural dynamics and reaction diversity. *Chem. Soc. Rev.*, 2008, 37, 2609–2619.

TUNGSTEN AND THE EVOLUTION OF LIFE

We go back 4.5 billion years to the infant earth. The early earth was shaken by volcanoes and electrical storms. In a painting of the eruption of Vesuvius by the English artist Joseph Wright (**Figure 5**) we see gases being emitted, the brightness, the energy. These gases are considered to be the source of the primitive atmosphere –water, carbon dioxide, nitrogen and possibly methane, but no oxygen. Energy for the chemical reactions leading to the first cells was provided by the sun and by flashes of lightning.

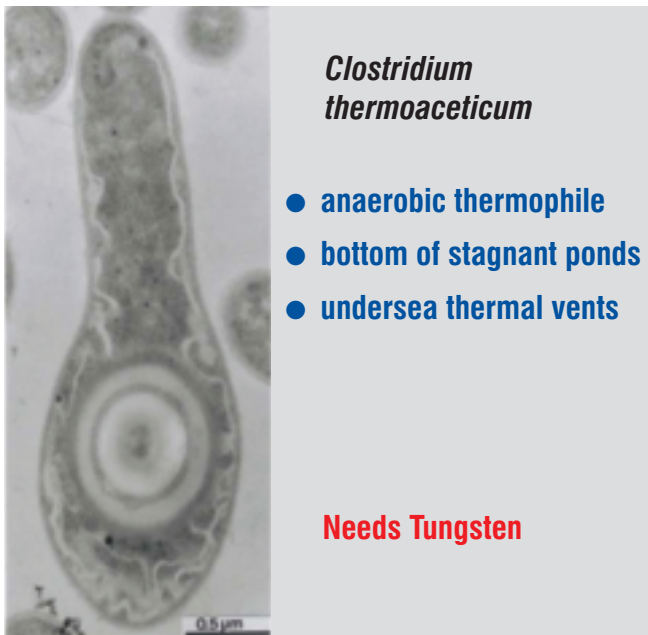


Figure 3: The bacterium *clostridium thermoaceticum* an anaerobe and thermophile, stable above 64 °C and tungsten-dependent.

Drake, H.L. and S. L. Daniel, *Research in Microbiology*, 2004, 155 422–436.
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Volcano



Figure 5: Joseph Wright of Derby. An Eruption of Mount Vesuvius, with the Procession of St. Januarius's Head. 1778.
The Pushkin Museum of Fine Art, Moscow, Russia.

One idea is that life began in a chemical soup, a warm pond. (**Figure 6**) However, the early earth with its burning sun, volcanoes and lightning was extraordinarily inhospitable. Molecules synthesised in reactions in the atmosphere and in shallow ponds would be destroyed by the intense ultraviolet radiation from the sun: there was no protective ozone layer. So the idea of a warm pond as the place where life began on earth has given way to the idea that life began in the ocean depths where the rays of the sun could not penetrate, near *hydrothermal vents*.

<http://www.ceoe.udel.edu/deepsea/level-2/geology/vents.html>

Russell, M.J. and Hall, A.J. The emergence of life from iron monosulphide bubbles at a submarine hydrothermal redox and pH front. *J. Geol. Soc. London*, 1997 154, pt 3, 377-402.

Martin, W., & Russell M.J.. On the origin of biochemistry at an alkaline hydrothermal vent. *Philosophical Transactions, Royal Society of London* 2007 (Ser.B) 362, 1887-1925

Martin, W., Baross, J., Kelley, D. & Russell, M.J.. Hydrothermal vents and the origin of life. *Nature Reviews, Microbiology*. 20086, 805-814.

Carbon dioxide reacts with hydrogen

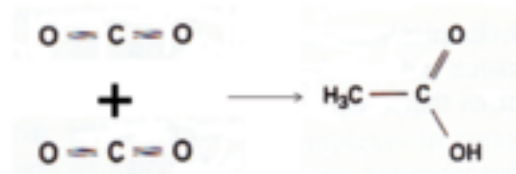


Figure 4: Carbon dioxide reacts with hydrogen to give acetic acid forming a carbon-carbon bond.

The Beginning of Life a chemical soup

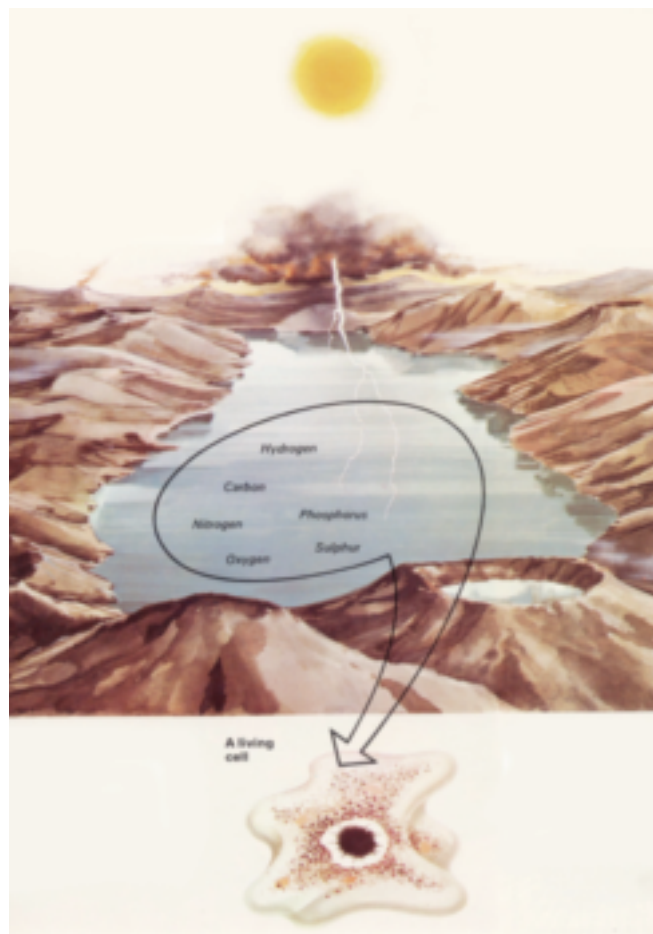


Figure 6: A warm pond, a chemical soup - where life began?

Adapted from Ramona-Ann Gale, *Prehistoric Life*, Macdonald Educational, London, 1973, p.3

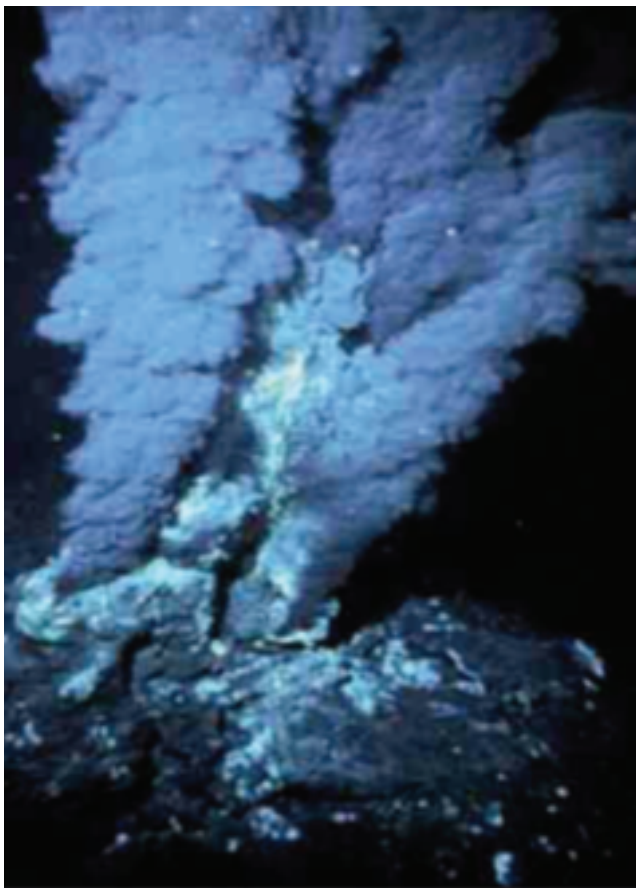


Figure 7: Black smoker at a mid-ocean ridge hydrothermal vent.

Hydrothermal vents support a variety of archaea. The discovery of the archaea in extreme environments suggests that life evolved under hellish conditions.

Credit: P. Rona. US National Oceanic and Atmospheric Administration (NOAA). Office of Ocean and Atmospheric Research (OAR)/National Undersea Research Program (NURP) 2010

HYDROTHERMAL VENTS

A hydrothermal vent is a geyser on the seafloor, a hot spring which ejects superheated water and steam (**Figure 7**). Seawater seeps into crevices in the ocean floor and is heated by the molten rock beneath the Earth's crust. The super-heated vent water rises and bursts through the seafloor generating a plume of steam and minerals known as a chimney. The hottest vents are called "black smokers"; they discharge iron and sulfide, which combine to form black iron monosulfide. The hot vent water is rich in minerals that help to support primitive bacteria and other organisms. Methane and ammonia are abundant in hydrothermal vent regions. Tungsten is concentrated relative to molybdenum in a hydrothermal vent; for example in the North Pacific Ocean the tungsten and molybdenum concentrations in the submarine hydrothermal fluid at 1400 m depths are: W, 3 $\mu\text{g/kg}$; Mo, 0.5 $\mu\text{g/kg}$; and in the ocean: W, 0.01 $\mu\text{g/kg}$; Mo, 10 $\mu\text{g/kg}$.

In the extreme conditions of the hydrothermal vents we find *extremophiles* (organisms that thrive in geochemically extreme conditions). They include thermophiles of the type found in the 'Grand Prismatic Spring' of Yellowstone National Park, the archaea and primitive bacteria. These primitive organisms, nearly 4 billion years old, require tungsten. So we think that these primitive organisms, capable of converting carbon dioxide to organic compounds with the aid of tungsten, represent early life on the infant earth. So we think of tungsten being associated with, indeed essential for, the development of life on earth. **Figure 8.**

Nitschke, Wolfgang and Russell Michael J. Just Like the Universe the Emergence of Life had High Enthalpy and Low Entropy Beginnings *Journal of Cosmology*, 2010, Vol 10, 3200-3216. <http://journalofcosmology.com/Abiogenesis101.html>.

Kishida K, Sohrin Y, Okamura K, Ishibashi J, Tungsten enriched in submarine hydrothermal fluids *Earth and Planetary Science Letters* 222, 819-827 (2004)

TUNGSTEN AND MOLYBDENUM - ADAPTING TO OXYGEN

The evolution of life according to the geological and fossil record is summarised in **Figure 9**. The earth was formed by the accretion of particles 4.5 billion years ago. The atmosphere was dominated by carbon dioxide and nitrogen. Before oxygen life consisted of thermophilic bacteria dependent on tungsten. After the development of an oxygen atmosphere and the growth of plants and animals, molybdenum took over from tungsten as one of the metals essential for plants and animals.

The scientist most associated with the evolution of life is, of course, Charles Darwin, **Figure 10**. The changeover from tungsten to molybdenum as a central element of life is an example of *adaptation*—here, chemical adaptation. With oxygen in the atmosphere, those organisms which adapted to the oxygen environment, which were able to use oxidised compounds, were the organisms which survived and flourished. These organisms found that molybdenum provided them with the chemistry they needed, as in the reduction of nitrate and the fixation of nitrogen, both molybdenum-dependent processes. In a sense tungsten is primitive and molybdenum is modern.

TUNGSTEN - DEPENDENT ENZYMES

The tungsten which some bacteria need is a constituent of the enzymes which control their chemistry. An *enzyme* is a biological catalyst: it speeds up a chemical reaction and sends it in a desired direction to products. How an enzyme works is shown in **Figure 11**. The conversion of reactants to products can go directly or via the enzyme. In the reaction path via the enzyme, a molecule interacts with the enzyme; it binds at the *active site*, that region of the enzyme where the chemistry takes place; and then converts to products. The reaction via the enzyme is faster than the direct reaction and selective.

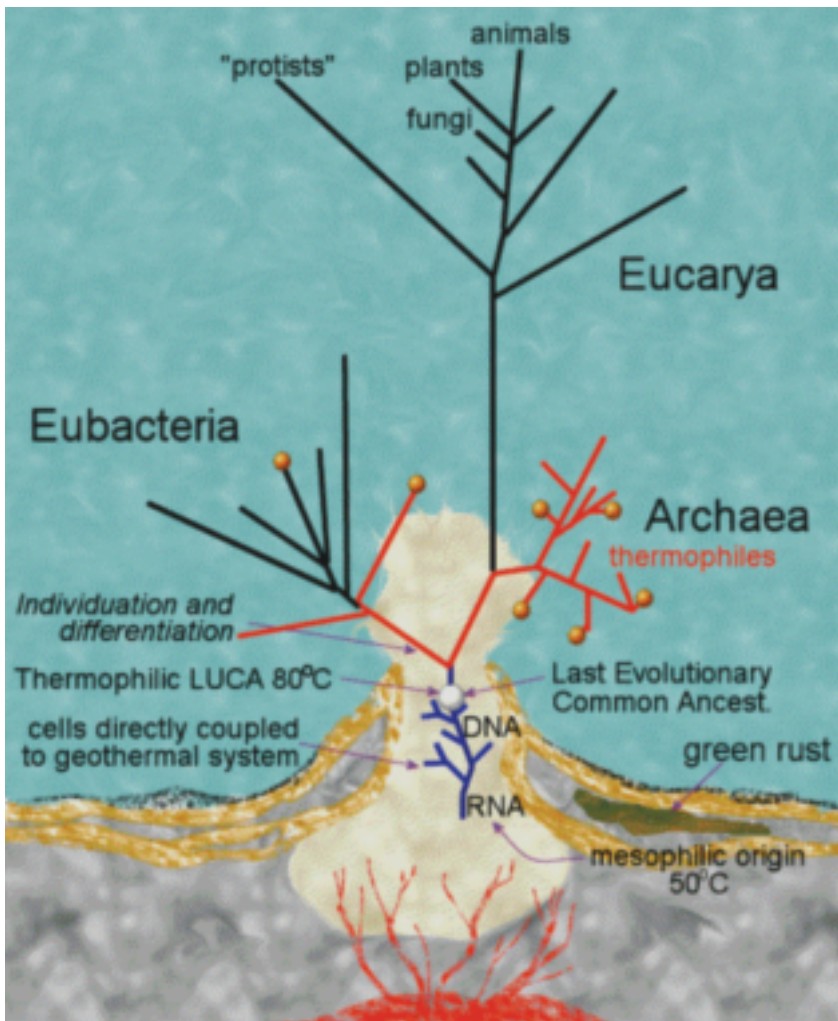


Figure 8: Major events that may have occurred at hydrothermal vents. Initially, the first cells are thought to have been a component of the geothermal system (i.e., actually part of the rock without cell membranes). The first pathways developed in these "organisms".

<http://cas.bellarmine.edu/tietjen/RootWeb/Easy%20Archaeon.htm>

Evolution of Life on Earth

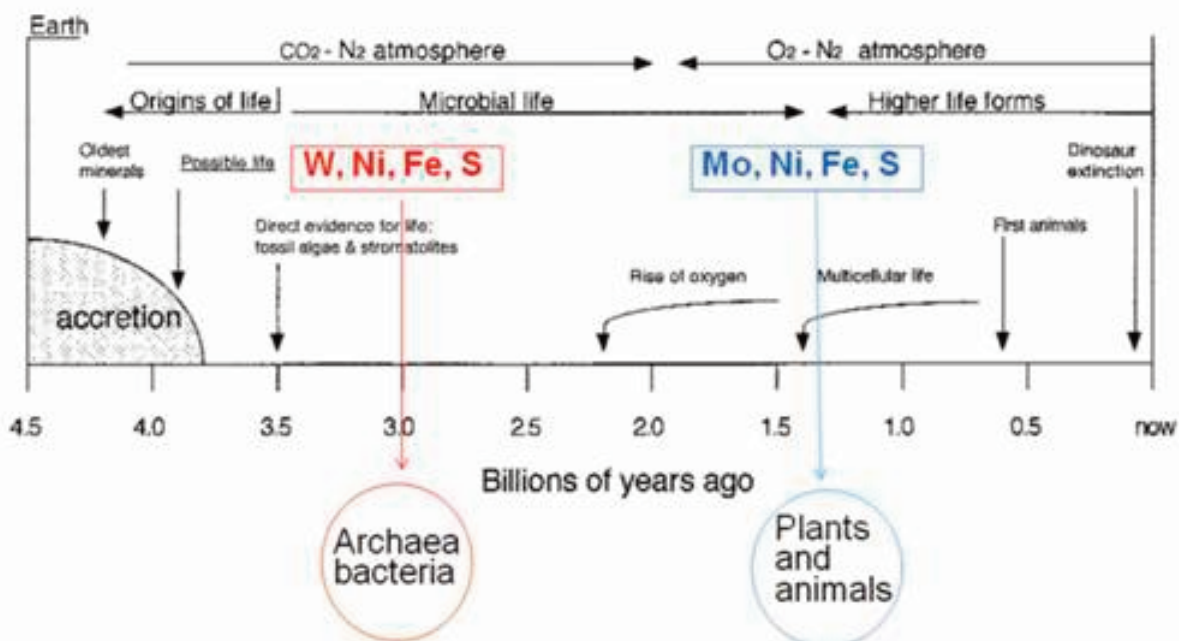


Figure 9: Life on Earth. The early atmosphere was dominated by carbon dioxide and nitrogen. Before oxygen life consisted of thermophilic bacteria dependent on tungsten. After the development of an oxygen atmosphere and the growth of plants and animals, molybdenum took over from tungsten as one of the metals essential for plants and animals.

McKay, C.P. and Davis, W.L. Planets and the Origin of Life in Weissman, P.R., McFadden, L.A. And Johnson, T.V.(eds.) Encyclopedia of the Solar System, Academic Press, London, 1999, p. 906, Fig. 4. Copyright Second Edition © 2007 Elsevier Inc.



Charles Darwin
1809 - 1882

Evolution by Natural Selection

On the Origin of the Species,
1859

"It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is most adaptable to change".

Adaptation is the evolutionary process whereby an organism becomes better able to live in its habitat

Figure 10: Natural selection and adaptation

How an Enzyme Works

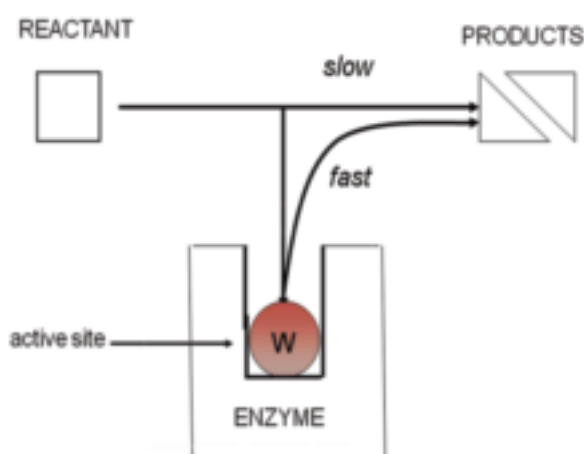


Figure 11: An enzyme speeds up a chemical reaction and sends it in a desired direction to products. The reaction can go directly or via the enzyme. Via the enzyme, a molecule interacts at the active site and then converts to products. The reaction via the enzyme is faster than the direct reaction and selective.

First enzyme shown to be tungsten-dependent Formate dehydrogenase

From bacterium *clostridium thermoaceticum*

Formate is end-product of many bacterial fermentations

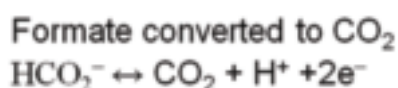
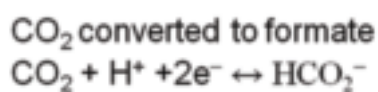


Figure 12: Formate dehydrogenase

In the 1970s, it was discovered that tungsten stimulated the growth of certain bacteria which produced methane and acetate. By the 1990s, it was known that tungsten is central to the carbon metabolism of thermophile bacteria and archae, their ability to use and make carbon compounds. Tungsten is needed because it is an essential constituent of the enzymes which the bacteria use.

FORMATE DEHYDROGENASE

The first enzyme shown to be tungsten-dependent was *formate dehydrogenase* from the bacterium *clostridium thermoaceticum*, **Figure 12**. When sodium tungstate is added the activity is increased; the effect of tungstate is greater than molybdate, **Figure 13**. Both cause an increase but tungstate is greater.

The structure of formate dehydrogenase determined by x-ray crystallography is shown in **Figure 14**. We see a tungsten atom encapsulated by proteins. When we zoom in on the tungsten atom we see it bonded to sulfur and selenium. Tungsten is at the active site of the enzyme.

ACETYLENE HYDRATASE

The x-ray structure of another tungsten-dependent enzyme, *acetylene hydratase*, shows a reactant molecule at a tungsten active site. This enzyme catalyses the addition of a water molecule to acetylene giving acetaldehyde (**Figure 15**). In the x-ray structure we zoom in on the tungsten atom. We see the channel along which the acetylene is funnelled to the active site of the enzyme. The acetylene interacts with a water molecule bound to tungsten at the active site.

TUNGSTEN AND CARBON DIOXIDE

Carbon dioxide is well known as a greenhouse gas, contributing to the earth's global warming. We can dispose of carbon dioxide by burying it. We can also use it as a starting point for chemical synthesis. One reason for trying to understand how tungsten enzymes work is to see if we can exploit their chemistry to make substances for catalysing reactions of carbon dioxide. Another way is to use a tungsten enzyme directly. The tungsten enzyme formate dehydrogenase attached to graphite has been proposed as an electrocatalyst for the reduction of carbon dioxide to formate (**Figure 16**). The graphite electrode transfers electrons via an iron-sulfur cluster to formate dehydrogenase. The enzyme reaction takes place under ambient conditions and is one-hundredfold faster than on any other catalyst; it is selective with formate as the only product. The reverse reaction can be used for the generation of electrical energy in a fuel cell.

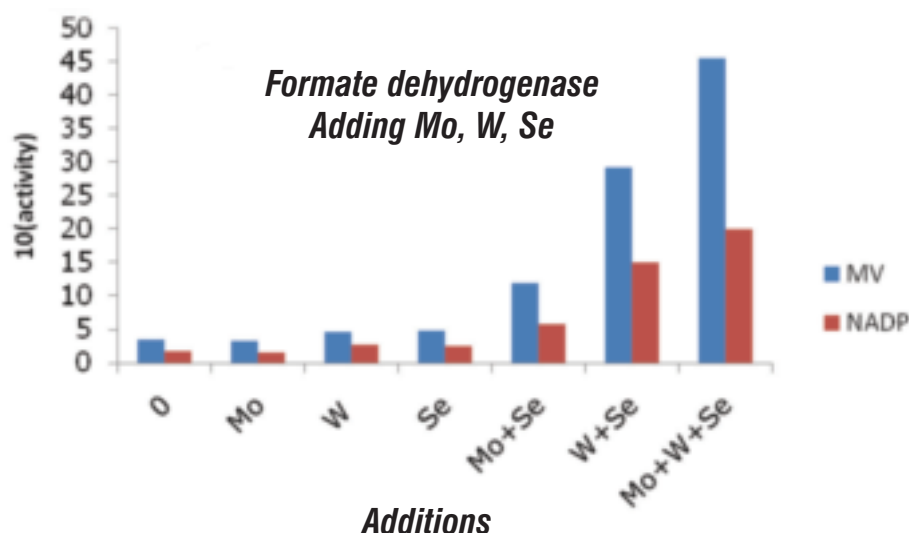


Figure 13: Enhancement of the activity of formate dehydrogenase by tungstate.

A unit of activity is the amount of enzyme which catalyzes the formation of 1 micromol of NADPH (2 electrons per mole) or 2 micromol of methylviologen (1 electron per mole) per min. Plotted from Andreesen, J.R. and Ljungdahl, L.G., *Journal of Bacteriology*, 1973, 116, 867-873. Formate dehydrogenase of *Clostridium thermoaceticum*: incorporation of selenium-75, and the effects of selenite, molybdate and tungstate on the enzyme.

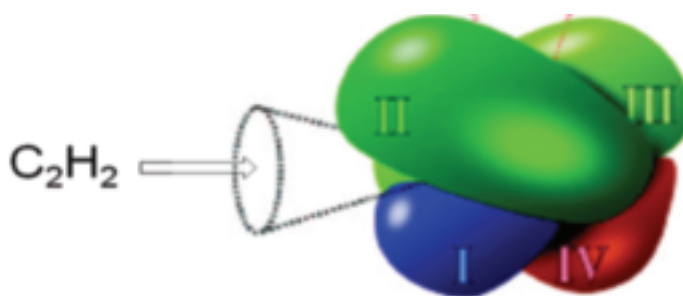
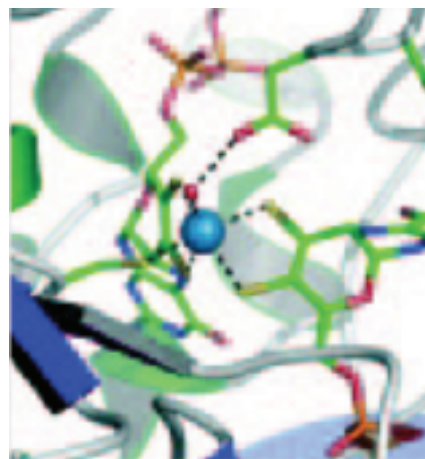
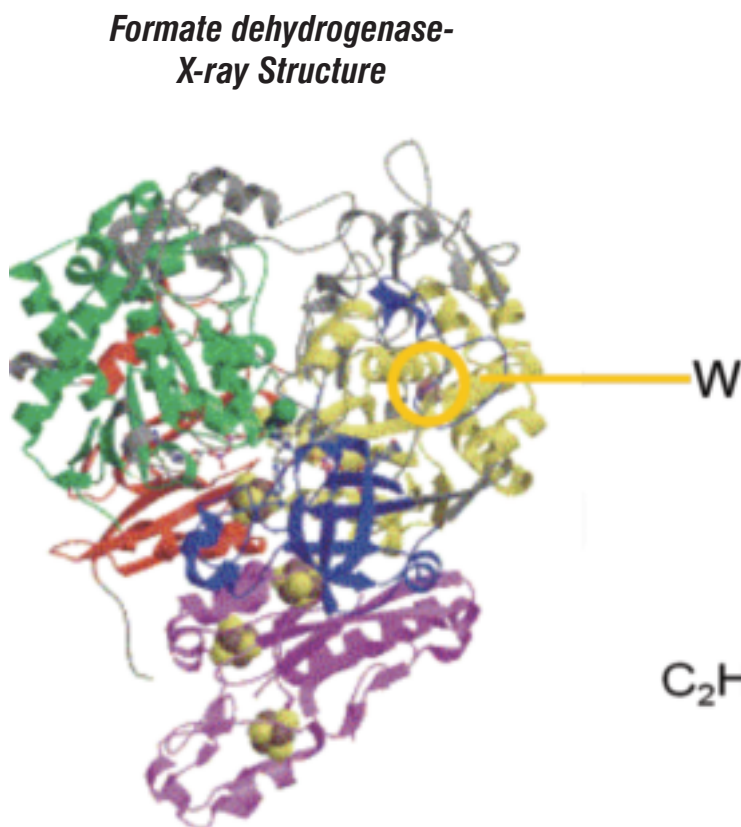


Figure 14: X-ray crystal structure of formate dehydrogenase showing the bulk structure and the location of the tungsten atom. The atoms binding the tungsten atom are 4S, 1Se and 10 of OH. The coloured ribbons represent sheets of proteins.

(<http://www.chemguide.co.uk/organicprops/aminoacids/proteinstruct.html>). Raaijmakers, H., Macieira, S., Dias, J.M., Teixeira, S., Bursakov, S., Huber, R., Moura, J.G., Moura, I. and Romano, M.J., *Structure*, 2002, 10, 126.

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Figure 15: Acetylene hydratase. X-ray structure showing the tungsten atom (top) and the channel along which the acetylene is funnelled to the active site (bottom). The tungsten atom is bound to 5S and 10 of a water molecule. An acetylene molecule interacts with the water molecule bound to tungsten at the active site.

Seiffert, G.B., Ullmann, G.M., Messerschmidt, A., Schink, B., Kronecker, Peter, M.H., and Einsle, O. *PNAS*, 2007, 104, 3073-3077.

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CO₂ Sequestration and Reduction - Electrocatalysis by Formate Dehydrogenase

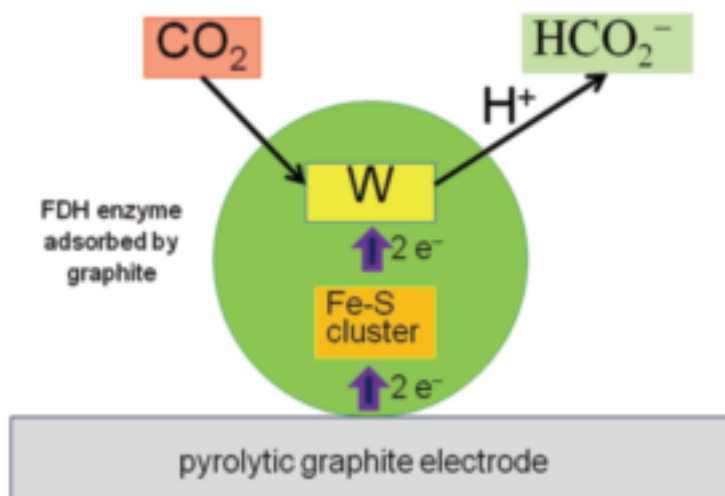


Figure 16: Electrocatalytic reduction of carbon dioxide by formate dehydrogenase on graphite.

Adapted from T. Reda, C. M. Plugge, N. J. Abram, and J. Hirst, PNAS, 2008, 105, 10654–10658 : Reversible interconversion of carbon dioxide and formate by an electroactive enzyme.

TUNGSTEN CHEMISTRY

To understand the role of tungsten in life we must do some chemistry.

We start tungsten chemistry with Fausto de Elhuyar, **Figure 17**, who discovered tungsten in 1783. He separated tungsten from wolframite (wolfram), iron manganese tungstate, the ore of tungsten. We recall that earlier, in 1781, the Swedish chemist Peter Hjelm had isolated molybdenum from molybdenite, molybdenum disulfide.

COMPARING TUNGSTEN AND MOLYBDENUM

Earlier I referred to molybdenum taking over from tungsten as an example of natural selection. Let us see how this works. In Mendeleev's Periodic Table (**Figure 18**) molybdenum and tungsten are associated-both in Group VI. They are transition elements, having variable oxidation states and forming complexes. Molybdenum is essential for life. In seeking to understand tungsten in life, it is helpful to make comparison with molybdenum.

It is noteworthy in comparing molybdenum and tungsten that the ores of tungsten, wolframite and scheelite, are tungsten-oxygen compounds with tungsten in oxidation state VI while the ore of molybdenum is molybdenum disulfide, molybdenite, having molybdenum in oxidation state IV and bound to sulfur (**Figure 19**). Molybdenum apparently prefers sulfur and a lower oxidation state. Nevertheless their compounds are similar – the oxides, the oxysalts and the sulfides, **Table 1**.

Fausto Elhuyar, discoverer, with his brother Juan José, of Tungsten in 1783



Figure 17: Fausto de Elhuyar who discovered tungsten in 1783 from the mineral wolframite (wolfram).

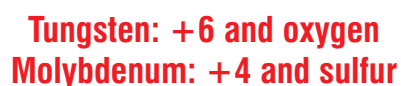
For the history and discovery of tungsten see the publication 'Tungsten: the Past, Present, Future', International Tungsten Association (ITIA), 2009.

Oil painting of Fausto de Elhuyar (Vienna 1788); Biblioteca Nacional de España – donation of Doña Isabel de Elhuyar in 1866 to the Consejo Minería (Junta Facultativa).

Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Period																			
1	H																	He	
2	Li	Be											B	C	N	O	F	Ne	
3	Na	Mg											Al	Si	P	S	Cl	Ar	
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr	
5	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe	
6	Cs	Ba	*	Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
7	Fr	Ra	**	Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cp	Uut	Uuq	Uup	Uuh	Uus	Uuo
			*																
			*	La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb		
			**																
			**	Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No		

Tungsten in the Periodic Table.

Tungsten and molybdenum like the neighbouring rhenium in their highest oxidation states form tetrahedral oxoanions $[\text{MoO}_4]^{2-}$, $[\text{WO}_4]^{2-}$, $[\text{ReO}_4]^-$. These species are only weakly oxidising unlike the oxoanions of the lighter elements, $[\text{CrO}_4]^{2-}$ and $[\text{MnO}_4]^-$, which are strongly oxidising. Molybdenum and tungsten enter into biology as the oxoanions which in a sequence of subsequent reactions become bound to sulfur and selenium at the active sites of molybdenum and tungsten-dependent enzymes.



A. Mottana, R. Crespi, G. Liborio, *The Macdonald Encyclopedia of Rocks and Minerals*, 1983.

Oxidation state	Compounds			
	oxides	oxosalts	sulfides	other
V1	MoO ₃	Na ₂ MoO ₄ .2H ₂ O		
	WO ₃	Na ₂ WO ₄ .2H ₂ O		
1V	MoO ₂		MoS ₃ * MoS ₂	
	WO ₂		WS ₃ WS ₂	WC

9.

REDUCTION OF TUNGSTATES AND MOLYBDATES

We can get a feeling for the differences between molybdenum and tungsten chemistry from experiments which are described in the older analytical chemistry textbooks.

To solutions in water of sodium molybdate and sodium tungstate we add hydrochloric acid and tin(II) (stannous) chloride. With both molybdate and tungstate a blue colour develops due to partial reduction of molybdenum(VI) and tungsten(VI) to molybdenum(V) and tungsten(V). Tin(II), a reducing agent, is able to reduce both molybdenum(VI) and tungsten(VI). (The blue colours are due to the mixed oxidation state (Mo(V,VI), W(V,VI)) compounds molybdenum blue and tungsten blue.)

If we use iron(II) (ferrous) chloride rather than tin(II) chloride we again obtain a blue colour with molybdate *but not with tungstate*. Iron(II) is a weaker reducing agent than tin(II). Iron(II) is able to reduce molybdate but not tungstate.

These simple experiments show that tungstate is less readily reduced than molybdate – or is less oxidising than molybdate. Conversion to a lower oxidation state requires less energy for molybdate than for tungstate and is also faster. We can quantify these qualitative observations with reference to the reduction potentials.

REACTIONS WITH HYDROGEN SULFIDE AND COMPLEXES

We now examine reactions with hydrogen sulfide. These are analytical reactions. We take solutions of molybdate and tungstate as

before, add tartaric acid to each, and bubble in hydrogen sulfide. We obtain a black precipitate, molybdenum trisulfide, with molybdate but no similar precipitate with tungstate. Tartaric acid is a complexing agent for both molybdate and tungstate. Evidently the tungstate-tartrate complex is less reactive towards hydrogen sulfide than the molybdate-tartrate complex. We might consider that tungstate is bound strongly by tartrate or that the tungstate complex reacts more slowly than the molybdate complex (or both).

TUNGSTATE AND MOLYBDATE COMPARED

The simple salts of molybdenum(VI) and tungsten(VI), for example sodium molybdate and sodium tungstate, contain the *oxoanions* $[\text{MoO}_4]^{2-}$ and $[\text{WO}_4]^{2-}$. They have the same structures (**Figure 20**). In both oxoanions the metal atoms are at the centre of a tetrahedron of oxygen atoms. Both ions carry a double negative charge. Their sizes are similar.

TUNGSTATE AND MOLYBDATE AND CARRIER PROTEINS

Molybdate and tungstate enter biology as the tetrahedral oxoanions: same structure, same charge, same size. Proteins have been isolated, so-called carrier proteins, which bind and transport tungstate and molybdate. Their x-ray structures show molybdate and tungstate encapsulated by the coiled protein chains (**Figure 21**). These carrier proteins transport molybdate and tungstate through cell walls into biological systems.

Structure of Tungstate $[\text{WO}_4]^{2-}$ and molybdate $[\text{MoO}_4]^{2-}$

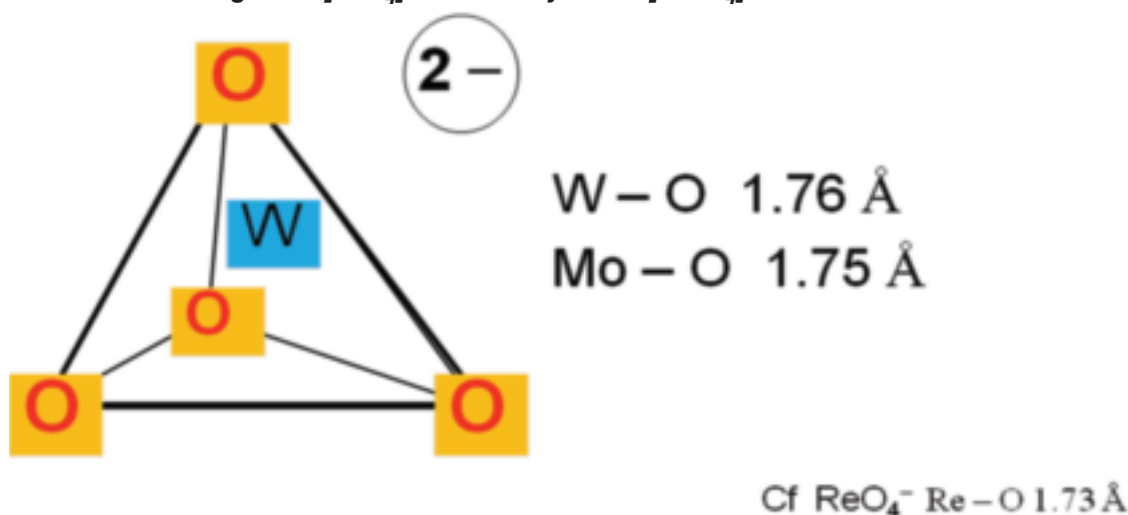


Figure 20: Structure of tungstate and molybdate and comparison with perrhenate. The metal atoms are at the centre of a tetrahedron of oxygen atoms.

NATURAL SELECTION OF TUNGSTEN AND MOLYBDENUM

What about the natural selection of tungsten and molybdenum? We can summarise it in this way. Tungsten compounds are more oxygen sensitive, they are more easily oxidised, they are more heat stable, and more reducing. Reactions are slower. And tungsten is more abundant in the ocean depths. We say that tungsten is better adapted to catalyse reactions near the limits of biology – in the absence of air, at high temperatures, and at low potentials. This is why tungsten was selected as the element of choice by primitive bacteria in the early evolution of life and is still so selected – by the thermophiles in the deep sea vents and for the reduction of carbon dioxide. Tungsten is primitive and molybdenum modern.

COMPETITION BETWEEN TUNGSTEN AND MOLYBDENUM

Let us now look at competition between tungsten and molybdenum. The enzymes *sulfite oxidase* and *xanthine oxidase* are molybdenum-dependent enzymes. The effect of adding tungstate to these enzymes is shown in **Figure 22**. As tungstate is added the enzyme activity decreases. Tungstate blocks or displaces molybdenum; it is an inhibitor.

Tungstate - Binding Protein

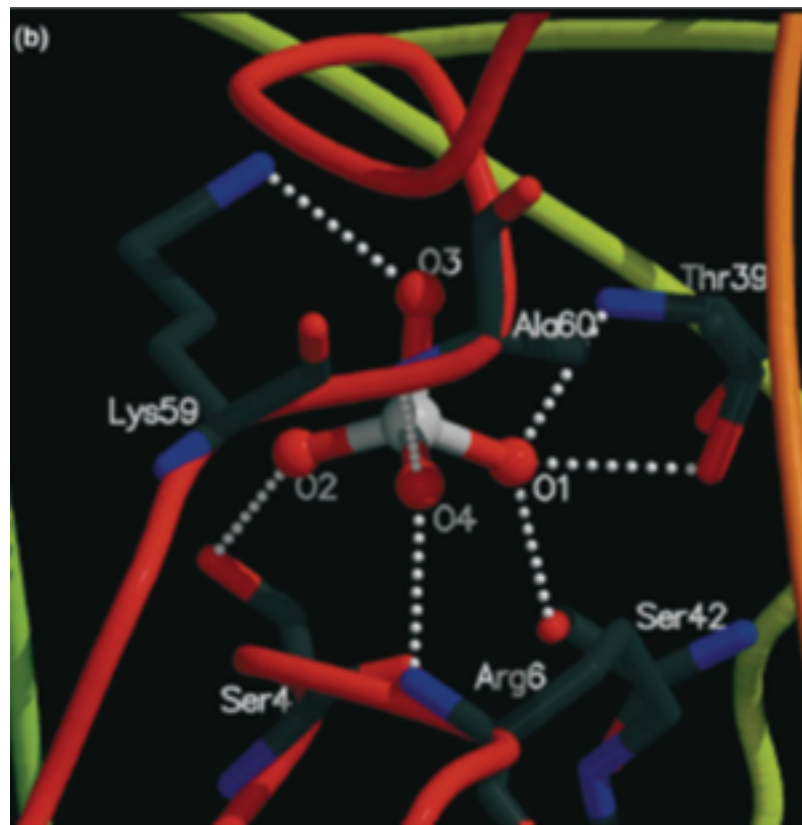


Figure 21: Tungstate bound in a carrier protein – a detail of the x-ray crystal structure. Tungstate is visible as the tetrahedral anion in the centre of the picture.

Wagner, U. G., Stupperich, E. and Kratky, C. *Structure*, 2000, 8, 1127–1136.
Structure of the molybdate/tungstate binding protein mop from *Sporomusa ovate*.
Copyright © 2000 Elsevier Science Ltd.

Tungstate decreases the activity of two Molybdenum enzymes

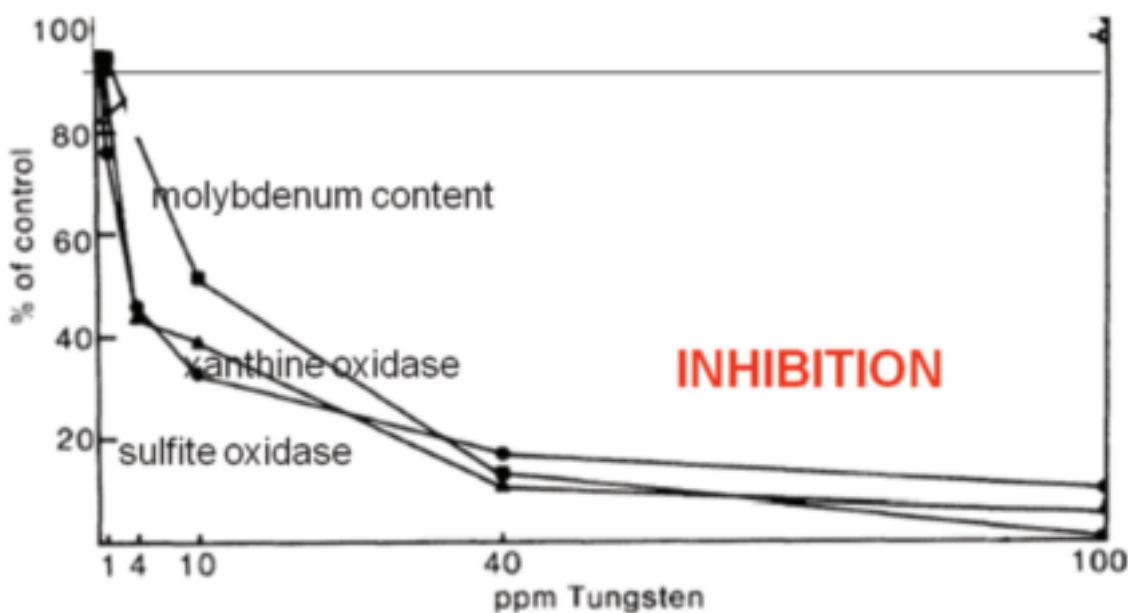


Figure 22: Effect of adding tungstate to the molybdenum-dependent enzymes xanthine oxidase and sulfite oxidase in rats.

Adapted from Cohen, H. J., Drew, R.T., Johnson, J. L. and Rajagopalan, K. V., *Proc. Nat. Acad. Sci. USA*, 1973, 70, 3655. Molecular-basis of biological function of molybdenum - relationship between sulfite oxidase and acute toxicity of bisulfite and SO_2 . Copyright (1973) National Academy of Sciences U.S.A

Reactions - Sulfite and Xanthine

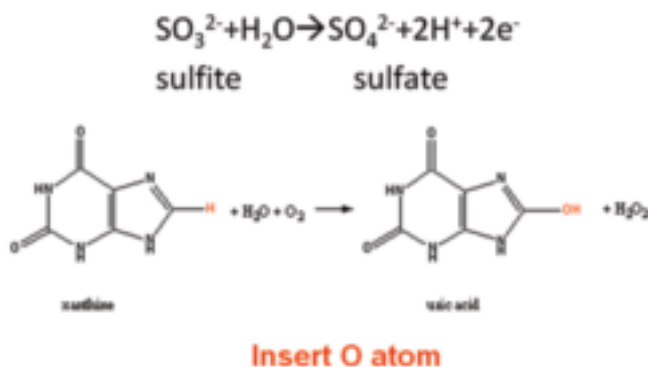


Figure 23: Reactions catalysed by the enzymes sulfite oxidase and xanthine oxidase.

Tungstate and Atherosclerosis

Development of atherosclerosis in mice treated with or without a western - type diet (WD) and tungstate.

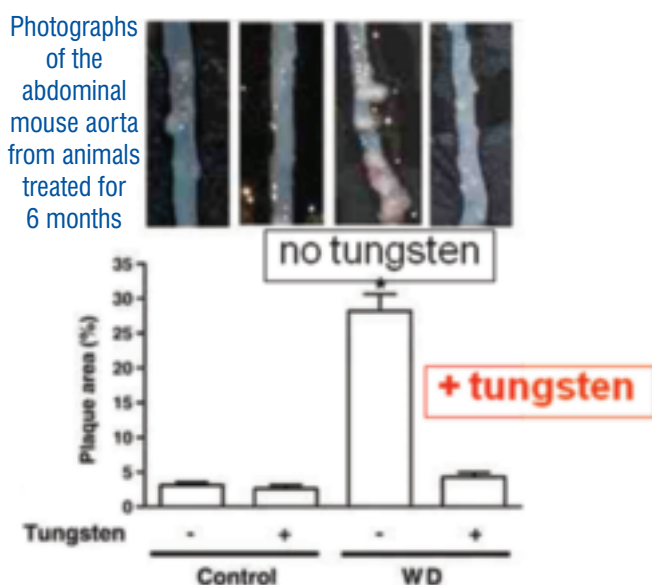


Figure 24: Tungstate is effective in preventing plaque formation.

Adapted from Schröder, K., Vecchione, C., Jung, O., Schreiber, J. G., Shiri-Sverdlov, R., van Gorp, P. J., Busse, R. and Brandes, R. P. *Free Radical Biology and Medicine*, 2006, 41, 1353-1360. Xanthine oxidase inhibitor tungsten prevents the development of atherosclerosis in ApoE knockout mice fed a Western-type diet.

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These enzymes transfer oxygen atoms – in sulfite oxidase, oxidising sulfite to sulfate; in xanthine oxidase, converting xanthine to uric acid by inserting a hydroxyl (OH) group in place of a hydrogen atom bonded to carbon (the reaction is on the pathway to the elimination of nitrogen compounds in metabolism), **Figure 23**. The essence of the chemistry is the insertion of an oxygen atom. Molybdenum does this by switching

between molybdenum(VI) and molybdenum(IV). The oxidation state change is more favourable for molybdenum (requiring less energy) and the oxygen-atom transfer is faster for molybdenum.

Mitchell, P. C. H., *Journal of Inorganic Biochemistry*, 1986, 28, 107-123.

Molybdenum in enzymatic and heterogeneous catalysis.

Tucci, G. C., Donahue, J. P., and Holm, R. H. *Inorg. Chem.*, 1998, 37, 1602. Comparative kinetics of oxo transfer to substrate mediated by bis(dithiolene)dioxomolybdenum and -tungsten complexes.

Davies, E. S., Aston, G. M., Beddoes, R. L., Collison, D., Dinsmore, A., Docrat, A., Joule, J. A., Wilson, C. R. and Garner C. D., *J. Chem. Soc., Dalton Trans.*, 1998, 3647–3656. Oxo-tungsten bis-dithiolene complexes relevant to tungsten centres in enzymes

Garner, C. D., Stewart, L. J. *Met. Ions Biol. Syst.*, 2002, 39, 699-726. Tungsten-substituted molybdenum enzymes.

Schulzke, C. J., *Chem. Soc., Dalton Trans.*, 2005, 713-720. Temperature dependent electrochemical investigations of molybdenum and tungsten oxobis(dithiolene) complexes.

TUNGSTATE AND MOLYBDATE IN SOIL

Potential toxicity of tungstate can be mitigated through differences in the binding abilities of tungstate and molybdate towards complexing molecules. The nitrogen fixing bacterium *Azotobacter vinelandii* present in soil requires molybdenum for its nitrogen-fixing enzyme nitrogenase. Tungsten is known to be toxic to nitrogen-fixing bacteria, partly by substituting for molybdenum in nitrogenase. Molybdenum and tungsten are present at about the same concentrations in soils (ca. 0.6–2.3 ppm). The relative uptake of molybdate and tungstate by bacteria is moderated by molecules (catechol siderophores) produced by *A. Vinelandii*. At high tungstate levels the concentration of these complexing molecules in the growth medium increases. They bind all the tungstate and molybdate as catechol complexes. However, molybdenum from the molybdenum-catechol complex is taken up by the bacteria much more rapidly than tungsten so allowing *A. Vinelandii* to satisfy its molybdenum requirement and avoid tungsten toxicity.

Wichard, T., Bellenger, J.-P., Loison, A., and Kraepiel, A. L. *Environ. Sci. Technol.*, 2008, 42, 2408–241. Catechol siderophores control tungsten uptake and toxicity in the nitrogen-fixing bacterium *Azotobacter vinelandii*.

MEDICAL APPLICATIONS OF TUNGSTEN - ACTUAL AND POSSIBLE

The chemistry leads us into some of the possible medical applications of tungsten compounds. I conclude with examples of the use, or possible use, of tungsten in medicine, see **Table 2**.

INHIBITION OF XANTHINE OXIDASE BY TUNGSTATE - ATHEROSCLEROSIS

Inhibition of xanthine oxidase by tungstate might possibly find application in the treatment of atherosclerosis. This condition is the blocking or hardening of blood vessels caused by plaques, the accumulation of fatty deposits and very much a feature of a Western-type fatty diet. It is found that tungstate is effective in reducing the formation of plaques, **Figure 24**. Mice are fed a Western-type diet with or without tungstate. In the control without the Western-type diet there is very little plaque. For mice fed a Western-type diet there

Table 2. Medical Applications of Tungsten

Substance	Application	Species	Reference
Tungsten carbide	Brain sensor implant to control prosthetics	Human	Hoyle, 2008
Sodium tungstate	Nuclear medicine as ^{188}Re generator Restenosis Hepatocellular carcinoma	Human	Knapp, 2005
Sodium tungstate	Free radical suppressor -atherosclerosis	Mouse	Schröder et al., 2006
Heteropolytungstates	Anti-viral, flu	Mouse	Liu et al., 2008
	Anti-tumour	Human	Hasenknopf, 2005
	Anti-bacterial	Human	Inoue et al., 2006
	Anti-bacterial	Human	Jelick-Stankov, et al., 2006

Hoyle, R. MicroBridge Services Ltd, Cardiff, UK, Medical Device Technology Nov/Dec 2008.

Knapp, F. F., Jr., http://www.ornl.gov/sci/nuclear_science_technology/nu_med/studies.html
Schröder, K., Vecchione, C., Jung, O., Schreiber, J. G., Shiri-Sverdlov, R., van Gorp, P. J., Busse, R. and Brandes, R. P. Free Radical Biology and Medicine, 2006, 41, 1353-1360. Xanthine oxidase inhibitor tungsten prevents the development of atherosclerosis in ApoE knockout mice fed a Western-type diet. Copyright © 2006 Elsevier Inc. All rights reserved. Permissions & Reprints

Liu, Y.-N., Shi, S., Mei, W.-J., Tan, C.-P., Chen, L.-M., Liu, J., Zheng, W.-J. and Ji, L.-N. Eur. J. Med. Chem., 2008, 43, 1963-1970. In vitro and in vivo investigations on the antiviral activity of a series of mixed-valence rare earth borotungstate heteropoly blues.
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Hasenknopf, B. Frontiers in Bioscience 10, 2005, 275-287. Polyoxometalates: introduction to a class of inorganic compounds and their biomedical applications.

Inoue, M., Suzuki, T., Fujita, Y., Oda, M., Matsumoto, N. and Yamase, Biochemistry, 2006, 100, 1225. Enhancement of antibacterial activity of methicillin-resistant and vancomycin-resistant Staphylococcus aureus.

Jelick-Stankov, M., Uskokovic-Markovic, S., Holclajtner-Antunovic, I., Todorovic M. and Djurdjevic, P. J. Trace Elements Med. Biol., 2007, 21, 8-16. Compounds of Mo, V and W in biochemistry and their biomedical activity.

is much more plaque but plaque is reduced for mice treated with tungstate. So tungstate is effective in preventing plaque formation. How is this? Tungstate inhibits xanthine oxidase activity and so diminishes the formation of peroxide which is responsible for plaque formation and fatty deposits. The effect of tungstate is dramatic. It is closely related to our understanding of tungsten and molybdenum chemistry.

TUNGSTATE IN NUCLEAR MEDICINE - $^{188}\text{RHENIUM}$

Sodium tungstate is used in nuclear medicine to deliver the ^{188}W isotope which by beta-decay converts to rhenium and then to osmium, **Figure 25**. ^{188}W is generated in a nuclear reactor. Tungsten oxide is dissolved in sodium hydroxide solution. The sodium tungstate so formed is absorbed on an alumina column and decays to perrhenate. It will be remembered with reference to the periodic table that rhenium has a diagonal relationship with molybdenum in that it forms a tetrahedral oxoanion. So the beta-decay of tungstate gives

perrhenate. ^{188}Re is a high-energy β -emitter. The high-energy radiation from ^{188}Re , used in a controlled manner, has been applied in bone pain palliation (temporary pain relief), bone marrow ablation (whereby human bone marrow cells are eliminated in preparation for a bone marrow transplant), in the unblocking of narrowed blood vessels, and in killing tumour cells, e.g. in the treatment of prostate cancer. ^{188}Re is said to be inexpensive. It can be 'milked' on demand from a $^{188}\text{W}/^{188}\text{Re}$ generator and is applied as a complex with HEDP (1-hydroxyethane-1, 1-diphosphonic acid). It offers the possibility of repeated therapy without additional costs and is attractive for use in developing countries.

Pandit-Taskar, N., Batra, M. and Chaitanya R. Divgi, C. R., Journal of Nuclear Medicine Vol. 45 No. 8 1358-1365. Radiopharmaceutical therapy for palliation of bone pain from osseous metastases.
Elder, R. C., Yuan, Jie, H., Helmer, B., Pipes, D., Deutsch, K. and Deutsch, E., Inorg. Chem., 1997, 36, 3055-3063 Studies of the structure and composition of rhenium-1, 1-hydroxyethylidenediphosphonate (HEDP). Analogues of the radiotherapeutic agent $^{186}\text{ReHEDP}$.

¹⁸⁸W in Nuclear medicine



Figure 25: Tungsten in nuclear medicine. Decay of ¹⁸⁸W (top) and nuclear synthesis of ¹⁸⁸W and ¹⁸⁸Re (bottom).

Tungsten Carbide Brain Implants

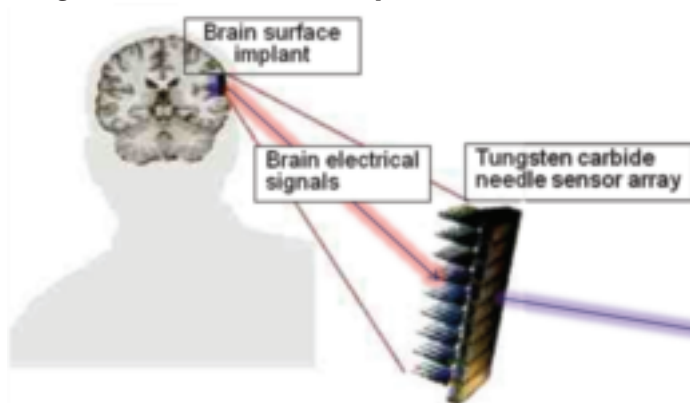


Figure 26: Tungsten carbide sensing electrical signals from the brain.

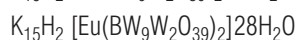
Adapted from: R. Hoyle MicroBridge Services Ltd, Cardiff, UK, Medical Device Technology November/December 2008 Copyright ©2008 Medical Device Technology P. Tathireddy and F. Solzbacher, Integrated Neural Interface Programme, Department of Electrical and Computer Engineering, University of Utah.

TUNGSTEN CARBIDE IMPLANT

Tungsten carbide, one of the most applied compounds of tungsten, noted for its hardness, has a potential medical application as a brain implant. Tungsten carbide needles are used as a sensor, as a brain implant which picks up electrical signals from the brain transmitting them to a control centre which enables the patient to manipulate prosthetics, **Figure 26**. This is an active research area. The attraction of tungsten carbide is that it is hard, durable and corrosion resistant and can be micro machined to fine needles.

HETEROPOLYTUNGSTATES - ANTIBACTERIAL AND ANTIVIRAL PROPERTIES

Heteropolytungstates have been reported to have antibacterial and antiviral properties, **Table 2**. For example, the mixed-valence rare earth borotungsto-heteropoly blues,



showed excellent antiviral activities against the influenza virus FluVB by inhibiting FluVB replication in mice.

Jellic-Stankov, M., Uskokovic-Markovic, S., Holclajtner-Antunovic, I., Todorovic, M., and Djurdjevic, P., Compounds of Mo, V and W in biochemistry and their biomedical activity, *Journal of Trace Elements in Medicine and Biology*, 2007, 21, 8-16.

Inoue, M., Suzuki, T., Fujita, Y., Oda, M., Matsumoto, N., and Yamase, T., Enhancement of antibacterial activity of beta-lactam antibiotics by [P₂W₁₀O₆₂]⁶⁻, [SiMo₁₂O₄₀]⁴⁻, and [PTi₂W₁₀O₄₀]⁷⁻ against methicillin-resistant and vancomycin-resistant *Staphylococcus aureus*, *Journal of Inorganic Biochemistry*, 2006, 100, 1225-1233.

Liu, Y. N., Shi, S., Mei, W. J., Tan, C. P., Chen, L. M., Liu, J., Zheng, W. J., and Ji, L. N., In vitro and in vivo investigations on the antiviral activity of a series of mixed-valence rare earth borotungstate heteropoly blues, *European Journal of Medicinal Chemistry*, 2008, 43, 1963-1970.

CONCLUSION

This account of tungsten in life and medicine has been challenging and wide ranging and, I hope, of some interest in describing the involvement of tungsten (often thought of as an exotic element) in life, how it relates to its chemistry, how it is different from and, in some ways, competes with molybdenum, and potential applications of tungsten in medicine.

For general accounts of tungsten and its compounds and applications see:

Tungsten: The Past, Present, Future. International Tungsten Industry Association (ITIA). 2009.

Tungsten: Properties, Chemistry, Technology of the Element, Alloys, and Chemical Compounds. Erik Lassner and Wolf-Dieter Schubert. Kluwer Academic/Plenum Publishers, New York. 1999.

Tungsten and its compounds. G.D. Rieck. Pergamon Press, London. 1967.

23rd ANNUAL GENERAL MEETING, VIENNA

Welcoming over 220 delegates from 27 different countries to the ITIA's 23rd Annual General Meeting, and warmly thanking CERATIZIT and Wolfram Bergbau for co-hosting the event, the President, Jesper Gullberg (Sandvik Tooling), said that delegates would have the honour to be joined by Dr Christoph Leitl, President of the Austrian Federal Economic Chamber, as the keynote speaker. The highly topical title of Dr Leitl's address was "Weathering Stormy Economic Times" in which he called for stronger regulations in the financial sectors, particularly within certain countries, to avoid a recurrence of a crisis caused by the uncontrolled flow of capital driven by speculation.

Gullberg noted that the first challenge for 2011 would be the search for a new Secretary-General to succeed the present incumbent who would be retiring at the end of March 2012.

Following the meeting, some 55 delegates visited Wolfram Bergbau's Mittersill mine in the Austrian Tyrol. Writing afterwards in his news service "Metal-Pages", Nigel Tunna, described how the mine, which produces scheelite, was located next to the "Hohe Tauern" National Park and Nature Reserve and close to skiing areas. The company operated to the highest environmental standards with the mine workings mostly underground and accessed by road directly through the side of the mountain. Most of the operations were automated, with crushing of the ore taking place underground before being transported 3km to the ore dressing plant by an underground conveyor. At the ore dressing plant, the ore was crushed and concentrated using froth flotation, with sound proofing ensuring that the noise of the processing was kept within the plant. The scheelite concentrate produced was sent to the

company's refining plant at St Martin where it was first processed to ammonium paratungstate (APT) and then into tungsten oxide and tungsten powders for the powder metallurgical industry.

Tunna concluded by describing the mine as the cleanest which he had ever visited in a long career.



Dr Leitl (right) with Jesper Gullberg (left) and Burghard Zeiler (centre).



Joie de vivre.....the newly elected Vice-President, **Claude Lanners** of CERATIZIT, joined by **Ulf Stromberger** and **Peter Hinterhofer** from Treibacher.

TUNGSTEN CONSORTIUM

- Compliance with REACH - a service from the ITIA

The last months of 2010 were hectic as the deadline of 30 November for registration of substances in the highest tonnage band approached, with consultation taking place within the SIEFs on identified uses, and agreement on classification and labelling. Guidance (tuition and videos) was provided to Consortium members on registration and IUCLID 5.2.

Finally, after four years of intensive work, the Lead Registrants have successfully submitted their registration dossiers to ECHA for the following six substances in the tonnage band >1,000tpa:

- ammonium paratungstate
- sodium tungstate
- tungsten blue oxide
- tungsten carbide
- tungsten metal
- tungsten trioxide

In addition, the registration of ferro-tungsten (tungsten and iron) was completed in conjunction with the Iron Platform.

Three substances in lower tonnage bands (ammonium metatungstate, fused tungsten carbide and tungstic acid) remain and the target is to register them also as soon as possible during 2011.

On the evidence to date, the Consortium is optimistic that none of these tungsten substances will require evaluation or authorisation.

During 2010, another company, Osram GmbH, joined the Consortium and conditions for the purchase of Letters of Access and the Recyclers' Agreement were published.

For further details of the Consortium work programme, a list of members and SIEF communications, please refer to the Consortium websites:

www.tungstenconsortium.com
and **www.sief.tungstenconsortium.com**

MEMBERSHIP

Welcome to:

- ▲ **Asia Tungsten Products Vietnam Ltd,**
a company which specialises in production and sales of ferro tungsten
- ▲ **Woulfe Mining Corp,**
a Canadian company which is re-developing the Sangdong tungsten-molybdenum mine in South Korea for the eventual production of scheelite concentrates, APT and tungstic oxide

ELECTION OF OFFICERS FOR 2011/12

The AGM unanimously approved the election of **Stephen Leahy** (CEO, North American Tungsten Corp Ltd) as President in succession to **Jesper Gullberg** (Sandvik Tooling AB) who had completed his two-year term and of **Claude Lanners** (General Manager, Purchasing & Human Resources, CERATIZIT SA) as Vice-President.

ELECTION TO THE EXECUTIVE COMMITTEE

The AGM unanimously approved the election of

- ▲ **Ms Christina Hallberg**
(Lead Buyer, Sandvik Tooling AB)
- ▲ **Mr Akihiko Ikegaya**
(Manager of Development Planning Dept, ALMT Corp)
- ▲ **Dr Andreas Lackner**
(President and CEO, Global Tungsten & Powders Corp)
- ▲ **Mr James Oakes**
(Vice President Technology, ATI Tungsten Materials)

ITIA's

24th ANNUAL GENERAL MEETING, 19-22 September 2011, Nice

Eurotungstène Poudres / Eramet will kindly host this meeting at the Radisson Hotel in Nice and the provisional programme is as follows:

Mon 19 September – Consortium Technical Committee Meeting
– Consortium Steering Committee Meeting

Tues 20 September – ITIA HSE Committee Meeting
– Joint Meeting of ITIA HSE and Executive Committees
– ITIA Executive Committee Meeting
– ITIA Reception and Dinner

Wed 21 September – ITIA AGM
– Tungsten Consortium Meeting
– Dinner hosted by Eurotungstène / Eramet

Thurs 22 September – ITIA AGM

Further details of this annual event, at which the worldwide industry gathers, will be posted to our website in late May, including a registration form. Companies which are not ITIA members may attend the AGM (there is a fee) and receive presentations on a variety of industry and general topics.

For a full list of ITIA members, contact details, and products or scope of business, please refer to the ITIA website - www.itia.info