Bioinorganic Vanadium Chemistry

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This book is printed on acid-free paper responsibly manufactured from sustainable forestry
in which at least two trees are planted for each one used for paper production.

This book is dedicated to my children
Miriam, Nadja, Matthias and Gunnar,
who helped me to comprehend life;
and to Renate,
in whom I found refuge and encouragement.

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Contents

Preface

In the mid-1980s, shortly after I was appointed to a professorship at Hamburg University, I was asked to offer graduate courses in Bioinorganic Chemistry, a discipline which only slowly gained ground in Europe, despite the fact that its importance and oncoming impact were well acknowledged. My knowledge of this new subject was close to zero, and therefore I decided to attend the 2nd International Conference on Bioinorganic Chemistry, which took place in summer 1985 at a very beautiful location, the Algarve on the Atlantic coast in southern Portugal. Among the many people I met was Hans Vilter (now in Trier), who had discovered the first vanadium enzyme, a vanadate-dependent bromoperoxidase isolated from a marine brown alga a few years before. Since vanadium has always been in the centre of my scientific life (my original research activities were directed towards organovanadium chemistry and vanadium-51 NMR), I became particularly interested, all the more as many of the attendees at the conference were not ready to take it that vanadium was actually an essential constituent of an enzyme. A couple of fruitful years of cooperation followed, and my research focus increasingly turned towards the biological aspects of vanadium, and finally became anchored in these grounds when I participated in a symposium on Marine Bioinorganic Chemistry ('MICBIC') in summer 1989. The symposium site was Heron Island, a tiny coral island in the Barrier Reef, off the shores of the Gold Coast in Australia. We walked across shallow waters, and I became acquainted with animals that I only vaguely remembered from biology lessons at school: the sea squirts, or ascidians. Kenneth Kustin (Brandeis University, Waltham, MA) spent some time introducing me to the unique ability of sea squirts to accumulate vanadate from sea water. I haven't done any research in this area, but remained pretty much interested in these vanadium-sequestering creatures. Consequently, one of the chapters in this book deals with ascidians, and I am greateful to Ken for having proof-read this specific issue. A year later, Achim Müller (University of Bielefeld) encouraged me to write a review article on 'The Bioinorganic Chemistry of Vanadium' for *Angewandte Chemie*. I did so (the article appeared in 1991 and had quite some impact) – and swore never to try to accomplish such a tedious task again. With the present book, *Bioinorganic Vanadium Chemistry*, I broke my oath.

Vanadium does still not (yet) cover the broad bio-spectrum pertinent to most of the other biologically relevant transition metals. One of the reasons arises from the fact that, so far, only two vanadium-dependent enzyme families are known, the vanadate-dependent haloperoxidases and vanadium nitrogenases (a third enzyme, a nitrate reductase depending on vanadium, still awaits confirmation). Additional biological implications of vanadium are scarce: apart from vanadium's presence in sea squirts (and fan worms), a naturally occurring vanadium compound, amavadin, has been found only in one additional genus of living organisms, the *Amanita* mushrooms, the most prominent representative of which is the fly agaric. In addition to these 'classical' bio-vanadium areas, there are interesting and highly promising novel developments when it comes to biological functions, and beneficial (i.e. medicinal) applications of vanadium. These new areas include bacterial energy recovery from vanadate, modification of proteins by vanadium and, of course, the potential of vanadium compounds in the treatment of diabetes mellitus. Both the 'classical' and the 'futuristic' themes are covered in detail in the present book. Vanadium compounds as insulin mimetics have been one of the focal areas within the European COST programme, and I am indebted to 'my' COST group

(D21-0009-01, 2001–2006) for the long, close and fruitful cooperation in a humanly and scientifically ambitious atmosphere, the results of which have been incorporated here.

A second reason for the sometimes hesitant examination and analysis of vanadium-related chemistry lies in the fact that the chemistry of vanadium is more 'touchy', or at least considered more touchy, than that of its neighbours (titanium, chromium and molybdenum). With a chapter directed towards the basics and the impact (for biological systems) of inorganic and coordination compounds of vanadium, I hope to have provided an overview of the biologically relevant crucial points, and to convince the prospective and the active researcher of the beauty of vanadium chemistry. This includes the main physical methods of characterisation of vanadium compounds in its biologically relevant forms. I have certainly been in close scientific contact with many colleagues committed to bioinorganic (vanadium) chemistry, contacts which have an enduring bearing on my own work in this field. I mention only two of them at this point, David Garner (School of Chemistry, Nottingham) and Vincent Pecoraro (University of Michigan, Ann Arbor), with whom I had critical discussions on a basis of fairness and equity, which has become pretty rare in the scientific community.

All of the findings in the biological chemistry of vanadium have their history. In order to appreciate and to value the impact of early perceptions and their protagonists, I have analysed a couple of early and original documents on, e.g., vanadium nitrogenase, vanadium in the blood of ascidians and vanadium compounds as a 'remedy' for a plethora of diseases. Snapshots of these historical events have been included. Included, in the first chapter, is also a detailed account on the discovery of vanadium.

The present book thus covers all of the main areas of the bioinorganic and related chemistry of vanadium. Not all of the relevant aspects could be accounted for in the same detail. In particular, this applies to areas which are – according to my subjective judgement – less intimately connected to the theme. In any case, I have tried to provide the reader with key references for most of these more peripheral areas.

It is hoped that this book will contribute to overcoming the barriers of comprehension between biochemists, inorganic chemists and chemists dedicated to environmental and health aspects of vanadium. The establishment of bi- to triannual symposia on the 'Chemistry and Biological Chemistry of Vanadium' a decade ago (the first one, held in Cancun, Mexico, in 1997, was organised by Debbie Crans, Colorado State University in Fort Collins, Co, and Alan Tracey, Simon Fraser University in Burnaby, BC) has provided considerable momentum in this respect.

A final remark concerning units: I have used SI units throughout, except in two cases, where other units have not become generally accepted in the subject-related literature: (1) for the molecular 'weight' (of proteins), the unit dalton (Da) is commonly used in biochemistry – and in the present book; (2) for bond distances, the ångström (Å) is favored by crystallographers and also employed here. All electrochemical potentials, if not provided relative to the normal hydrogen electrode (NHE) in the original literature, have been recalculated and refer to NHE $= 0$.

1 Introduction and Background

1.1 History

The discovery of the element vanadin, or vanadium as it is internationally known in its Latinised form, is as colourful as its chemistry.[1] On 22 January 1831, J. J. Berzelius wrote a letter to cheer up F. Wöhler,[2] who had missed discovering the new element by a hair's breadth, in which he told the following charming story to describe Wöhler's misfortune:[1]

> 'As to the sample you sent me, I want to tell you the following anecdote: In olden times the beautiful and charming goddess Vanadis lived up in the far north. One day, someone knocked on her door. The goddess remained comfortably seated and thought: Let whoever it is knock again; but there was no more knocking, and whoever had knocked went back down the steps. The goddess was curious to see who was so indifferent to being admitted, sprang to the window and looked at who was going away. Alas! she said to herself, that's that rascal [*Schalk*] Wöhler. Well, he surely deserves it; if he had been a little more concerned about it, he would have been admitted. The fella does not even look up to the window in passing by. After a few days, someone knocked on the door again, and this time, the knocking continued. The goddess finally came herself and opened the door. Sefström entered, and from this encounter Vanadin was born.'

The sample mentioned at the beginning of the anecdote was a specimen (a white powder) obtained by treatment of brown lead ore from the district Zimapán in central Mexico. The ore had originally been given to Baron von Humboldt by the Spanish mineralogist del Rio in Mexico on the occasion of Humboldt's visit there in 1803–04, and brought to the Museum für Naturkunde in Berlin by Humboldt in 1805.[3] A second sample of del Rio's brown lead ore was sent to the laboratory of Collet-Descotil in Paris. Collet-Descotil, who analysed the sample in 1805, came to the conclusion that the mineral contained chromium (which had been discovered in 1797). Wöhler began to investigate the brown lead ore in 1828 and noted that, in contrast to what had been established by Collet-Descotil, its properties did not match those of chromium. Wöhler became ill and stopped providing support for his findings. Later, he commented in a letter to Berzelius: 'I was an ass [*Ich war ein Esel*] not to have discovered [vanadin] two years before in the brown lead ore from Zimapán.'[1] Wöhler

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[1] Translation of the original letter (ref. [1]) adapted from ref. [2]; modified to match the original.

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was not the only one to fall short of discovering vanadium: during the winter of 1830–31, J. F. W. Johnston in England analysed a lead mineral from Wanlockhead, Scotland, and discovered a new substance resembling chromium. He became aware of its true identity while reading the letter of Berzelius to P. L. Dulong, presented at the Académie Royale in Paris on 7 February 1831.[4]

Meanwhile, Nils Gabriel Sefström, a physician and chemist, who taught chemistry at the School of Mines in Falun, Sweden, started, in the mid-1920s, to investigate a black powder obtained by treating bar iron from the Taberg with hydrochloric acid. The Taberg, rich in iron ore and the highest elevation in the province of Småland in South Sweden, rises up to 343 m (about 1000 ft). Sefström resumed his studies of the black powder in April 1830, discovering a substance which had certain properties in common with chromium and others with uranium. He soon found out that the substance contained neither chromium nor uranium,[5] but was something entirely new. The experiments were continued in Berzelius' laboratory, where the blue colouring of the lower oxidation states[2] of the new element was established as one of its peculiarities (*Eigenthümlichkeiten*).

In the course of this work, Sefström originally proposed the name *Odinium* for the new metal. Odin is the god of the winds in the Northern Germanic mythology (Wotan for the Southern Germanic tribes). But then, Sefström asked Berzelius to choose a better name than odinium because 'it fits so badly in French and English' ['*det passer så illa in franskan och engelskan*']. The new metal was thus provisionally re-named *Erian*, after Erianae[3], a by-name of Athena (= Minerva; see, e.g., Berzelius' letter to Wöhler of 27 December 1830[2]). Wöhler, in his answer to Berzelius (4 January 1831), used the name *Sefströmium*. Sefström finally chose the name vanadin ('*på latin Vanadium*'[4]) for the new metal, after *Vanadis*, an epithet of the Nordic[5] goddess Freya – Odin's wife,[5] the most aristocratic goddess in the Gothic mythology ['*den förnämsta gudinnam uti göthiska Mythologien*'],[5a] who symbolises beauty and fertility – essential features of vanadium chemistry. Vanadis (Figure 1.1) is usually illustrated, in a somewhat martial attitude, spear in hand on a chariot drawn by cats, animals which were sacred to the Northern Germanic tribes. An additional motivation for Sefström when choosing vanadin (or vanadium) arose from the fact that none of the elements known so far started with the letter V ['*... hvars begynnelse-bokstaf ej förekommer ... enkla kroppars namn*'].[5a]

In a second letter to Berzelius (9 January 1831), Wöhler enclosed the white powder sample mentioned above, suggesting that it might be Erianoxyde. Wöhler was eventually able to show that his sample (from the Zimapán ore) was identical with Sefström's new metal vanadin (from bar iron and slag thereof), which prompted G. Rose to add *Vanadinbleierz* (vanadium lead ore; actually vanadinite, $Pb_5[VO_4]_3Cl$, Figure 1.2, which is isomorphous with hydroxyapatite) to Humboldt's original label describing the Zimapán ore exhibited in the Berlin museum.[3]

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[2] Acidic solutions containing the hydrated vanadyl ion (VO^{2+}) are light blue.

[3] Actually Εργανη (Ergane), the patron of craftsmen and artisans. The Greek ergón (= energy, work), related to Ergane, is the root for the English 'work' (German and Dutch: Werk; Swedish: Verk).

[4] The title of the Swedish version of Sefström's new discovery actually reads *Om Vanadium, en ny metall, funnen uti stångjern, som är tillverkadt af malm ifrån Taberget i Småland* (On Vanadium, a new metal, found in bar iron which is manufactured from ore of the Taberg in Småland).[5a] The German pendant[5b] is entitled *Ueber das Vanadin ...* (On Vanadin ...).

[5] Old-Islandic *Vana-dis*, meaning woman from the *Vanir*, one of the two lineages of Gods in Norse mythology.

Figure 1.1
The Nordic goddess Vanadis, alias Freya.

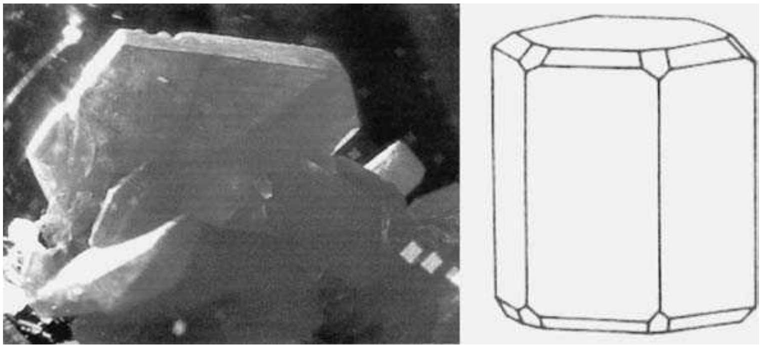

Figure 1.2
Crystals and crystal habit of (hexagonal) vanadinite, $Pb_5[VO_4]_3Cl$. The crystals are deep orange–red.

Poggendorf (Editor of *Ann. Phys. Chem.*) added a note to Sefström's key article on the discovery of vanadium[5b] in which he forestalls any allegations regarding the priority of Sefström's discovery, in particular with respect to del Rio's claim (which he later withdrew) to have discovered, in 1801–03, a new element in the brown lead ore from Zimapán.

Andres Manuel del Rio y Fernandez actually discovered vanadium when experimenting with the *plomo pardo de Zimapán* from the Cordonal Mine in Hidalgo. Fascinated by the differently coloured salts of the new element obtained in varying preparations, he called it *Panchromo*. A brief note on this discovery is contained in *An. Cienc. Nat.* (Madrid) **1803**, 6, 46: 'Panchromium. Novel metallic matter announced by Sñ. Manuel del Rio in a report from Mexico directed to Don Antonio Cavanillas, dated 26th September 1802.' Later, del Rio renamed the new element *Eritrono* (erythronium)[1] with reference to the red colour obtained when alkaline and alkaline earth metal salts of the new metal were heated or treated with acids. Since the properties of erythronium to some extent resembled those of chromium, del Rio lost confidence in his discovery, additionally discouraged by the slapdash analysis carried out by Collet-Descotils. He consequently noted that the supposed new element was nothing but chromium, factually renouncing his discovery. Del Rio later accused Humboldt of not having given his discovery its due attention and publicity, an essentially unjustified reproach, since papers documenting del Rio's experiments were lost at sea when, unknown to del Rio, the vessel carrying them to France was shipwrecked.[3]

From today's point of view, it appears strange that the obvious differences between the chemical behaviour of chromium and erythronium were overlooked in the experiments carried out by del Rio himself and by Collet-Descotil, a renowned chemist of his time: as ammonia is added to digested vanadinite, white ammonium vanadate is obtained (ammonium chromate is yellow). When heated, bright red V_2O_5 forms; when treated with acids, a red solution of decavanadate (essentially $[H_2V_{10}O_{28}]^{4-}$) is formed. The respective reactions with chromate yield greenish Cr_2O_3 and orange dichromate.

Berzelius, Johnston and others tried in vain to isolate the metal itself. The substances they thought were metallic vanadium, obtained by reduction of vanadium oxide with carbon or potassium, or of vanadium chlorides (VCl_3, $VOCl_3$) with potassium or ammonia, all turned out to be carbides, silicides, nitrides (VN) or low-valent oxides (VO).[4] The first apparently successful generation of metallic vanadium was accomplished by Sir Henry Enfield Roscoe in 1869 by reduction of VCl_2 with hydrogen in a lengthy experiment:[1]

> 'When he [Roscoe] heated the tube [containing VCl_2 in a platinum boat inside a porcelain tube], hydrochloric acid gas came off in torrents, and continued to be evolved in decreasing quantity for from forty to eighty hours. When it finally ceased to come off, the tube was cooled and the boat was found to contain a light whitish grey-coloured powder, perfectly free from chlorine.'

Roscoe himself described the grey-coloured powder in the following way:[6]

> 'Metallic vanadium thus prepared examined under the microscope reflects light powerfully, and is seen to consist of a brilliant shining crystalline metallic mass possessing a bright silver-white lustre. Vanadium does not oxidise or even tarnish in the air. ... The metal is not fusible or volatile at a bright red heat in nitrogen; the powdered metal thrown into a flame burns with the most brilliant scintillations. Heated quickly in oxygen, it burns vividly, forming the pentoxide. ... The specific gravity of metallic vanadium at 15 °C is 5.5 [actually, the density of vanadium is $6.11\,g\,cm^{-3}$]. It is not soluble in either hot or cold hydrochloric acid; strong sulphuric acid dissolves it on heating, giving a yellow solution. ... Fused with sodium hydroxide, the metal dissolves with evolution of hydrogen, a vanadate being formed.'

The first large-scale synthesis of 99.9% pure vanadium was carried out in 1927 by the Westinghouse Lamp Co. by heating a mixture of vanadic oxide, metallic Ca and $CaCl_2$ in an electric furnace to 760 °C. Nowadays, pure vanadium metal is obtained by reduction of V_2O_5 with calcium, or following the van Arkel/de Boer process (thermolysis of VI_3).

1.2 Occurrence, Distribution and Impact

Vanadium (element No. 23) is comparatively abundant in the universe. At 0.0001%, its cosmic abundance is comparable to that of copper and zinc. The cosmic abundance is, e.g., reflected in chondritic meteorites, which contain 220 atoms of the isotope ^{51}V in relation to 10^6 silicium atoms. Cosmic formation of vanadium is based on the α, γ cascade up to ^{52}Cr, followed by the reaction sequence[4]

$$^{52}\mathrm{Cr}(n, \gamma)^{53}\mathrm{Cr}(n, \alpha)^{50}\mathrm{Ti}(n, \gamma)^{51}\mathrm{Ti}(\beta^-, \gamma)^{51}\mathrm{V}$$

The isotope ^{51}V accounts for 99.75% of the naturally occurring isotopes. The remaining 0.25% is supplied by the isotope ^{50}V, whose cosmic formation is due to an electron-capture process by ^{50}Cr:

$$^{50}_{24}\mathrm{Cr} + \beta^- \rightarrow\ ^{50}_{23}\mathrm{V}$$

^{50}V is *very* mildly radioactive, decaying with a half life of 1.4×10^{17} years either by electron capture/positron emission (to generate ^{50}Ti; 83%) or via β^- decay (to form ^{50}Cr; 17%):

$$^{50}_{23}\mathrm{V} + \beta^- \rightarrow\ ^{50}_{22}\mathrm{Ti}\,/\,^{50}_{23}\mathrm{V} \rightarrow\ ^{50}_{22}\mathrm{Ti} + \beta^+ \quad \text{and} \quad ^{50}_{23}\mathrm{V} \rightarrow\ ^{50}_{24}\mathrm{Cr} + \beta^-$$

In the Earth's crust, vanadium is 22nd in abundance (0.013% w/w) and thus more abundant than copper and zinc. In sea water, commonly considered the cradle of life on our planet, the average concentration of vanadium, which is present mainly in the form of ion pairs $Na^+H_2VO_4^-$, is around 30 nM. Vanadium is thus the second most abundant transition element in marine environments, outmatched only by molybdenum [ca 100 nM molybdate(VI)]. Vanadium is supplied by riverine input; scavenging by vent-derived iron oxides helps to control the concentration and cycling of vanadium in the oceans.[7] The vanadium content of human blood plasma is around 200 nM; this ca 10-fold increase with respect to sea water points to its possible biological function. The vanadium level in tissue is even higher, averaging 0.3 mg kg^{-1} (ca 6 μM). Vanadium accumulates in bones, liver and kidneys.

Vanadium is a ubiquitous trace element. The average content in shales, which are particularly rich in vanadium, is 0.012% w/w. In sandstone and carbonate-based and magmatic rock, the vanadium content is lower by one order of magnitude. More than 120 vanadium-based minerals are known, containing the element in cationic and anionic form, and in the oxidation states III, IV and V. A cross-section representing these characteristics and the general inorganic chemistry of vanadium – which will be dealt with in Chapter 2 – is provided in Table 1.1. The most common minerals are vanadinite (Figure 1.2), patronite, roscoelite (vanadium mica), carnotite and descloizite.

Vanadium minerals are essentially formed in the course of geological processes. An epigenic formation of specific minerals is, however, conceivable: certain bacteria, such as *Pseudomonas vanadiumreductans*[8] and *Shewanella oneidensis*[9] (Figure 1.3), can use vanadate(V) as an external electron acceptor, reducing vanadate(V) to vanadium(IV) [and perhaps even further to vanadium(III)], and thus producing sherwoodite-like inorganic

Table 1.1 Selection of vanadium minerals with information on the nature of vanadium.

Mineral name	Formula	Oxidation state of vanadium	Type of compound
Karelianite	V_2O_3	III	Oxide
Roscoelite (vanadium mica)	$K(Al, V)_2(OH, F)_2[AlSi_3O_{10}]$	III	V^{3+} aluminosilicate
Häggite	$VO(OH) \cdot VO(OH)_2$	III and IV	Metahydroxide
Minasragrite	$VOSO_4 \cdot 5H_2O$	IV	Vanadyl salt
Simplotite	$Ca[V_4O_9]$	IV	Tetravanadate(IV)
Patronite	$VS_4 \equiv V(S_2)_2$	IV	Disulfide
Vanoxite	$2V_2O_4 \cdot V_2O_5 \cdot 8H_2O$	IV, V	Oxide
Sherwoodite	$Ca_9Al_2V_4^{IV}V_{24}^{V}O_{80} \cdot 56H_2O$	IV, V	Polyoxovanadate
Navajoitite	$V_2O_5 \cdot 3H_2O$	V	Oxide
Munirite	$Na[VO_3]$	V	Metavanadate
Steigerite	$Al[VO_4] \cdot 3H_2O$	V	Orthovanadate
Carnotite	$K(UO_2)[VO_4]$	V	Orthovanadate
Vanadinite	$Pb_5[VO_4]_3Cl$	V	Orthovanadate
Descloizite	$Pb(Zn, Cu)OH[VO_4]$	V	Orthovanadate
Chervetite	$Pb_2[V_2O_7]$	V	Divanadate
Barnesite	$Na_2[V_6O_{16}]$	V	Hexavanadate
Hummerite	$K_2Mg_2[V_{10}O_{28}]$	V	Decavanadate
Sulvanite	$Cu_3[VS_4]$	V	Thiovanadate

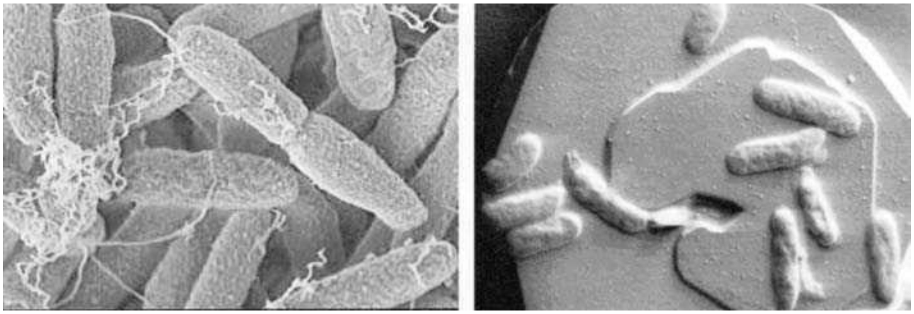

Figure 1.3
Scanning electron microscopy images of the soil bacterium *Shewanella oneidensis* (strain MR-1). The picture on the right shows the bacterium on haematite (Fe_2O_3).

deposits. The composition of the mixed-valence (V^V/V^{IV}) mineral sherwoodite is given in Table 1.1. This issue will be resumed in more detail in Section 4.5.

Another source of vanadium, of interest in biological and environmental contexts, are fossil 'fuels' such as peat, coal, bitumen, oil-shales, asphalts and crude oil. The vanadium content of hard coal can vary from 0.007 to 0.34%. Crude oil from Albania (0.034%), the Volga–Ural region (0.061%) and Venezuela (0.12%) (upper limit in all three cases) is particularly rich in vanadium.[4] A high vanadium content is often associated with high sulfur contents. The reasons for the notable enrichment of vanadium in fossils compared with bio-mass precursors such as bacteria, protozoans, algae, plants and animals are still under debate. Possible mechanisms for a secondary input of vanadium in decaying material include accumulation by phenolic compounds formed by degradation of lignin, by humic substances, and absorption from ground water, in particular in areas where the ground water is enriched by weathering of vanadium containing minerals and rocks. Anoxic conditions appear to promote vanadium absorption, possibly because of the very low solubility of vanadyl (VO^{2+})[6] hydroxides at a pH of around 7. In the case of crude oil, accumulation of vanadium may also be traced back to vanadium scavenging as oil passes through sediments rich in vanadium. Crude oil contains various porphinogens, derived from chlorophylls and haems of decayed marine organisms. Porphinogens are excellent complexing agents for the vanadyl cation. Most of the vanadium contained in carbonaceous sedimentary rock, asphaltene/kerogene[10] and geologically young oil is in fact present in the form of vanadyl porphyrins;[11a] see, e.g., the chlorophyll-derived complex in Figure 1.4. Old oils contain most of the vanadium in non-porphinogenic compounds,[11b] examples of which are also shown in Figure 1.4.

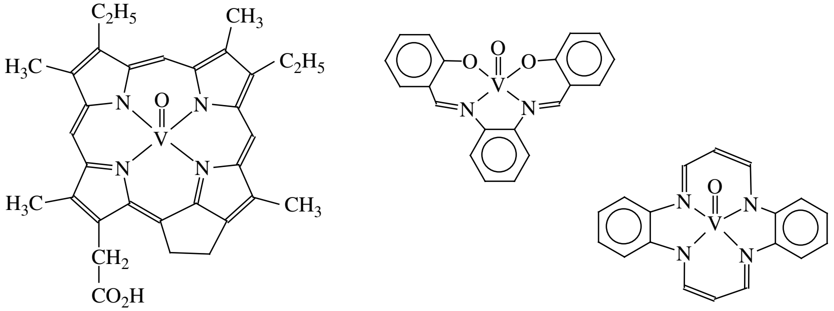

Figure 1.4
Examples of vanadyl compounds in crude oil. Left: porphinogenic (vanadyldesoxiphyllerythrin); middle and right, non-porhinogenic.

In the course of refining crude oil, vanadium becomes enriched in the high molecular mass asphaltenes. Processing and combustion of fossil fuels convert the organic vanadium compounds into vanadium oxides (V_2O_4 and V_2O_5), which are, at least in part, emitted into the atmosphere, where they catalyse the conversion of sulfur dioxide to sulfur trioxide and thus promote the formation of sulfuric acid, one of the components of acid rain. Other industrial activities, such as the production of ferrovanadium (used in the fabrication of particularly strong and durable steels), ceramics containing vanadium oxide and vanadium oxide-based catalysts add to the anthropogenic emission, as do leachates and effluents from mining and milling. The overall loadings caused by human activities to land, oceans and the atmosphere is, however, considerably less than that resulting from other sources and events.[12] Vanadium pollution is therefore not a global problem, but can have an impact in metropolitan and industrialised areas.

The vanadium content of normal food and drinking water is in the ppb to ppm region and thus well below any toxic level. Exposure to vanadium, e.g. by inhaling vanadium pentoxide, or from elevated vanadate levels in food and drinking water, does constitute a health risk. Inhaled particulate vanadium can induce oxidative stress and thus damage the

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[6] Throughout, the term ‘vanadyl’ will only be used for $V^{IV}O^{2+}$, i.e. *not* for the corresponding vanadium(V) fragment $V^{V}O^{3+}$.

respiratory epithelial cells and provoke inflammatory and fibronic lung injuries. High-risk exposure includes mining and milling of vanadium-bearing ores, and particulate vanadium and vanadium oxide accompanied by, e.g., vanadium-based catalyst production. Fly ashes as a result of combustion processes may also contain high loadings of V_2O_5. The established value for immediate danger to life or health is $70\,\mathrm{mg\,m^{-3}}$ V[13] and the maximum allowable concentration (MAC) of V_2O_5 in the working environment is $0.05\,\mathrm{mg\,m^{-3}}$ (8-hour time-weighted average, 40-hour week). Table 1.2 summarises LD_{50} and LC_{50} values for oral and inhalatory administration of vanadium oxides (V_2O_5, V_2O_3) and metavanadate ($K/NH_4[VO_3]$) to rats.[14] The LD_{50} value indicates the level of a harmful substance (in mg per kg body weight) causing the death of 50% of the test animals within a defined period of time, commonly 14 days. The LC_{50} is the corresponding indicator for lethal concentration in air. There are therefore no substantial differences in the toxicity of the vanadium(V) compounds. V_2O_3, on the other hand, is relatively nontoxic. *Dermal* (skin) contact with the vanadium oxides and metavanadates appears to be harmless. A more detailed account of the physiological effects of vanadium is included in Chapter 5.

Table 1.2 LD_{50} and LC_{50} values[a] for vanadium oxides and metavanadates administered to rats[14].[b]

	LD_{50} ($\mathrm{mg\,kg^{-1}}$ b.w.) (oral administration)	LC_{50} ($\mathrm{mg\,l^{-1}}$) (inhalative administration)
V_2O_5	221–716	2.2–16.2
V_2O_3	>3000	>6.65
$K[VO_3]$	314–318	1.85–4.16
$NH_4[VO_3]$	141–218	2.43–2.16

[a] See text for definition.

[b] Ranges reflect differences in response due to sex and (V_2O_5) particle size.

The first applications of vanadium go back to Berzelius, who observed that an extract from gallnuts, when treated with small amounts of ammonium vanadate, yielded a deep-black liquid, which makes excellent ink.[4] Wöhler noted, however, that the letters written with this ink faded and were barely legible after a couple of years (the recipe was later improved by Hélouis, who used tannin instead of gallnut preparations). The use of vanadium in oxidation catalysis, viz. the formation of aniline black from aniline, dates back to the mid-1870s. Aniline black is a black dye used to stain cotton and leather, and obtained by oxidation of aniline. The catalytic potential of vanadium pentoxide was discovered in 1895 in the context of the use of V_2O_5 in the oxidation of toluene and benzaldehyde.[15] Nowadays, vanadium oxides are established oxidation catalysts in the production of sulfuric acid and maleic anhydride. Mixed ester–chlorides of the hypothetical orthovanadium acid (H_3VO_4) of the general composition $VOCl_n(OR)_{3-n}$ (where R represents an alkyl residue) are sporadically applied in polymerisation reactions of alkenes, and low-valent vanadium compounds can act in reduction catalysis.[16] About 80% of the world production of vanadium goes into ferrovanadium. Ferrovanadium contains ca 50% vanadium; it is manufactured by reduction of vanadium and iron oxides with coal and serves as an additive for specialised steels. Promising fields of future impact are catalytic applications of nanoscopic vanadium pentoxide materials (including nanowires/nanorods and nanoporous materials), vanadium redox batteries (employing the V^V/V^{IV} and V^{III}/V^{II} couples) and lithium/silver vanadium oxide batteries.

Objective evidence for the presence of vanadium in plants was provided by E. O. von Lippmann in 1888,[17] and this period may be considered the entrée into the biological chemistry of vanadium:

> 'An even rarer element, which can accumulate in sometimes considerable amounts in charred slop, obtained in the course of manufacturing molasses [from sugar-beet], is vanadin, perceivable by its noticeable colourations, usually blue or blue–grey. The percentage of this matter present in charred slop cannot be minor, since I succeeded, already eight years ago, to separate from selected samples [of charred slop] . . . ca 1.5 g of pure sodium vanadate (*vanadinsaures Natrium*).'

The first to start simple experiments on the influence of vanadium on the growth of bacteria, germinating seeds, fungi and infusorians and the response of animals (frogs, pigeons, rabbits, guinea pigs, dogs and cats) towards vanadate was John Priestley[18][7] (not to be mistaken for Joseph Priestly, famous for his co-discovery (with Scheele) of the element oxygen, or with the writer John B. Priestley). 'The salt used in this research was tribasic sodium vanadate [Na_3VO_4], obtained by fusing a mixture of three molecules of sodium carbonate with one molecule of vanadium pentoxide.' While the germination of lettuce seeds was not affected by 0.1% solutions of sodium vanadate, it was totally prevented by 1% solutions. The elaborate descriptions of his animal experiments, which were injected lethal doses, read like horror stories. Excerpt from the protocol on a cat:

> '3h.15m. [after injection]: Very feeble; may be handled with impunity. Respirations rapid, and heart extremely feeble. 3h.15m: Rolls over two or three times, as if in pain; breathing very rapid and shallow. Rises but cannot stand; lies on its side, stretches out its four paws, and seizes with them the bars of its cage. Slight opisthotonos. Right posterior extremity drawn forward. Great dispnoea apparently. Moans. 3h.20m: On touching the cornea, the eye was not closed. Dead.'

The amount of vanadate applied to the cat, which 'was small and adult', corresponded to 250 mg V_2O_5 (!), i.e. two to three orders of magnitude more than used nowadays in the treatment of diabetic animals.

Vanadium preparations containing substantially lower and thus subtoxic levels of vanadium were applied as early as 1899 for the treatment of anaemia, tuberculosis, chronic rheumatism and diabetes mellitus. A blend of vanadium salts and sodium chlorate, named *Vanadin*, was traded as a prescription against syphilis.[4] The tradition of using vanadium compounds as a restorative goes back to the beginning of the last century. Commercially available preparations containing vanadyl sulfate, such as *Vanadyl Fuel*, are nowadays popular among body builders because they purport to increase muscle mass. Since vanadyl is precipitated in the form of insoluble hydroxides under the slightly alkaline conditions in the small intestine, it is barely absorbed. Absorption from the gastrointestinal tract averages 0.1–1%,[13] rendering vanadyl sulfate preparations harmless – as long as these preparations do not contain chromium compounds as additives. In Japan, a mineral water from the Fuji region is on the market as*Vanadium Water* (Figure 1.5), which is supposed to act as a general tonic; it contains an innocent 54 μg of vanadium per litre.

The biological importance of vanadium was definitely established when in 1911 M. Henze reported on *Untersuchungen über das Blut der Ascidien* [Investigations on

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[7] J. Priestley, *Philos. Trans. R. Soc. London* **1876**, *166*, 495–498

Figure 1.5
Vanadium water from the Fuji region contains ca 50 μg vanadium (in the form of hydrogenvanadate) in 1 litre. Inscriptions on the left-hand image: top line, 'The natural water created by Fujisan gave [us] a marvel'; bottom left, 'Super ions magic water (*hadosui*)'; bottom right, 'Ground-water from the basalt bed/Fujisan vanadium water'.

the Blood of Ascidians], of the Mediterranean sea squirt *Phallusia mamillata*.[19][8] Henze obtained a deep-blue precipitate from aqueous lysates of the ascidians' blood cells which, upon evaporation with nitric acid, yielded vanadium pentoxide. Henze also noted the high acidity of the lysates, without establishing the identity of the acid (actually sulfuric acid), which he originally assumed to be of organic nature. Nor was he able to reveal the nature of the vanadium {$[V^{III}(H_2O)_5HSO_4]^{2+}$; see Section 4.1} present in the vanadocytes, the vanadium-containing blood cells. Being aware of the potential of vanadium(V) compounds in oxidation catalysis, Henze proposed an analogous role for the vanadium containing 'chromogen' in oxygen activation. The function of vanadium in ascidians is still an enigma to date.

The next milestones in the biological chemistry of vanadium are listed chronologically below:

1933–36	H. Bortels: Discovery of the role of vanadium in nitrogen fixation.
1972	E. Bayer: Isolation of *amavadin* from the fly agaric.
1977	L. J. Cantley: Discovery of the role of vanadate as an efficient inhibitor of ATPases.
1983	H. Vilter: Isolation of the first vanadium enzyme, vanadate-dependent bromoperoxidase, in the marine alga *Ascophyllum nodosum*.
1986	Sussex Nitrogen Fixation Group: Isolation of a vanadium nitrogenase from *Azotobacter*.
Since ca 1980	Development of vanadium compounds for the treatment of diabetes mellitus.

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