Metals and Life

Edited by Eleanor Crabb and Elaine Moore

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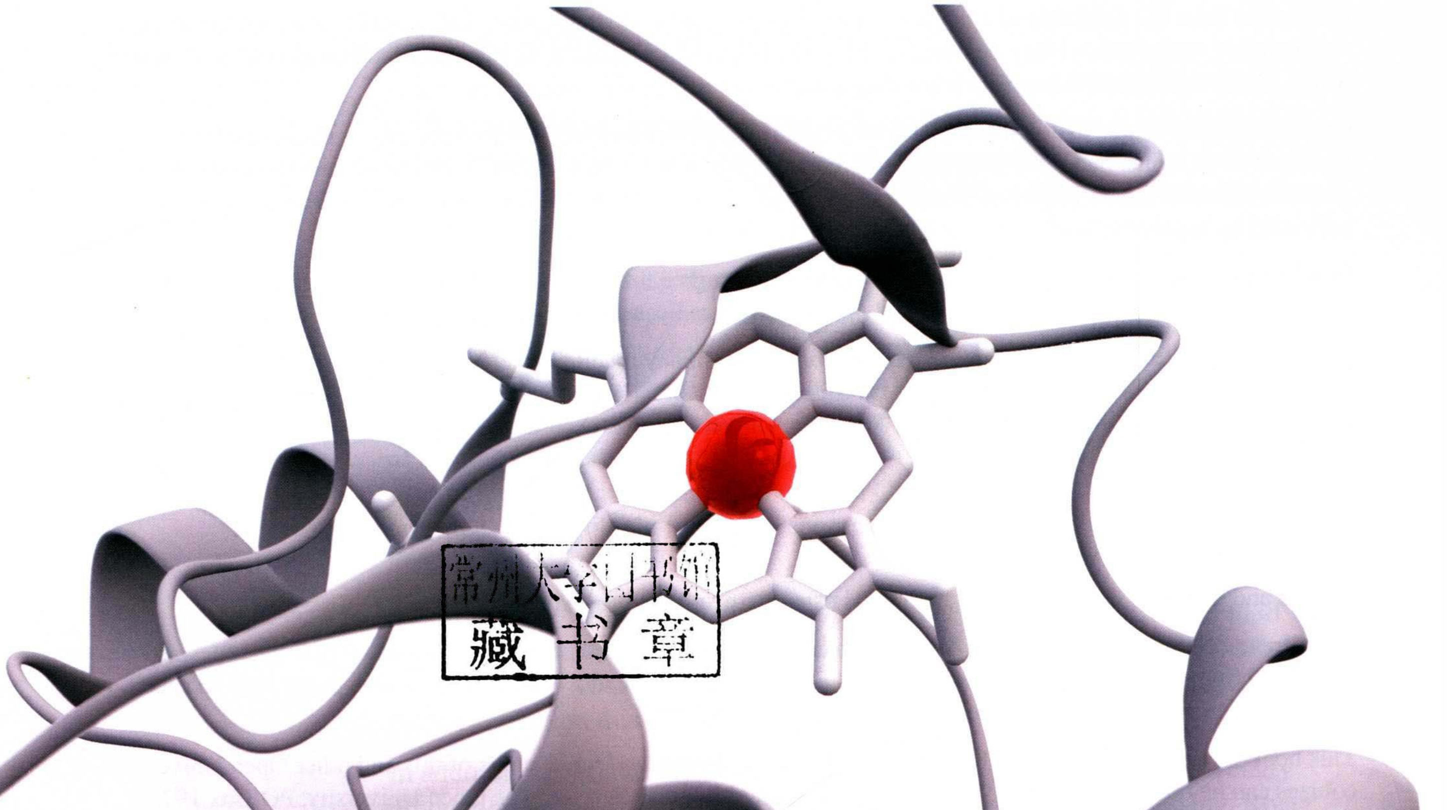

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Metals and Life

Metals and Life and *Concepts in Transition Metal Chemistry* have been written as part of the Open University course S347 Metals and Life and are designed to work as stand-alone textbooks for readers studying them either as part of an educational programme at another institution, or for self-directed study.

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Preface

This book aims to provide an introduction to the fascinating field of bioinorganic chemistry.

We begin by introducing you to the metals essential for life, and the functions that they fulfil in the physiology of animals. These metals primarily exist as complexes and so the second chapter looks at a number of ligands of biological importance. (Prior study in inorganic chemistry, in particular coordination chemistry, is assumed, together with an appreciation of the techniques used to the characterise metal complexes and proteins.) Following this introduction, we then move on to consider the methods that organisms employ to acquire metal ions, transport and store them. This leads on to a discussion of biomineralisation, important in the formation of bone and teeth. Later chapters introduce you to the roles that metals play in biology and some of the key processes involving 'metalloproteins'. The final chapter (which is delivered online) uses excerpts from textbooks in the RSC eBook collection and embedded videos to consider the role that metals play in medicine, in the diagnosis and treatment of disease, as well as the effects of metal toxicity and deficiency.

A few words now about the layout and style of the text. At various points in the book, you will find 'boxed' material; this provides background information or enrichment materials outside the scope of the main narrative. You will also find important terms highlighted in **bold** font in the text at the point where they are first defined, and these terms are also bold in the index.

Active engagement with the material throughout the book is encouraged by the use of questions incorporated into the text, indicated by a square (■), followed immediately by our suggested answer. In addition, further questions testing your understanding of the materials are included on the website associated with this book (indicated in the text by the icon). If you are studying this book as part of an Open University course you should visit the course website. If you are not reading this book in conjunction with an Open University course of study, further resources are available from the accompanying website by visiting www.rsc.org/metalsandlife.

We would like to thank the many people who helped with the production of this book. In addition to the principal authors, Joan Mason and Kiki Warr contributed to the text. We would also like to thank the authors of the books in the RSC eBook collection that are referred to in Chapter 9.

In addition we would like to thank all those involved in the Open University production process, Margaret Careford for her careful word processing, Roger Courthold for transforming our rough sketches into colourful illustrations, Chris Hough for cover design and artwork, Hazel Carr, Yvonne Ashmore and Judith Pickering for managing the whole process and to our editor Rebecca Graham whose help in the editing of this book, is very gratefully acknowledged. We would like to thank our External Assessor, Professor Kieran Molloy, University of Bath and critical readers, Dr Ruth Durant, University of the West of Scotland, Dr Christine Gardener and Dr Susan Dewhurst, whose detailed comments have contributed to the structure and content of the book. Finally, we are delighted that this book is being published in association with RSC Publishing.

Contents

1 Introduction

At first sight the idea of inorganic chemistry associated with life may appear to be a rather narrow field of study, as we tend to think of living matter as being just organic (even suggested in the name 'organic' chemistry). However, it is a fact that without certain inorganic elements no organism could exist.

Figure 1.1 shows a 'biological Periodic Table'. The elements that are known to be essential in biochemical systems for a wide range of plants, animals or bacteria are shown in orange and blue, with those thought to be essential or possibly essential for only some species in pink and green respectively.

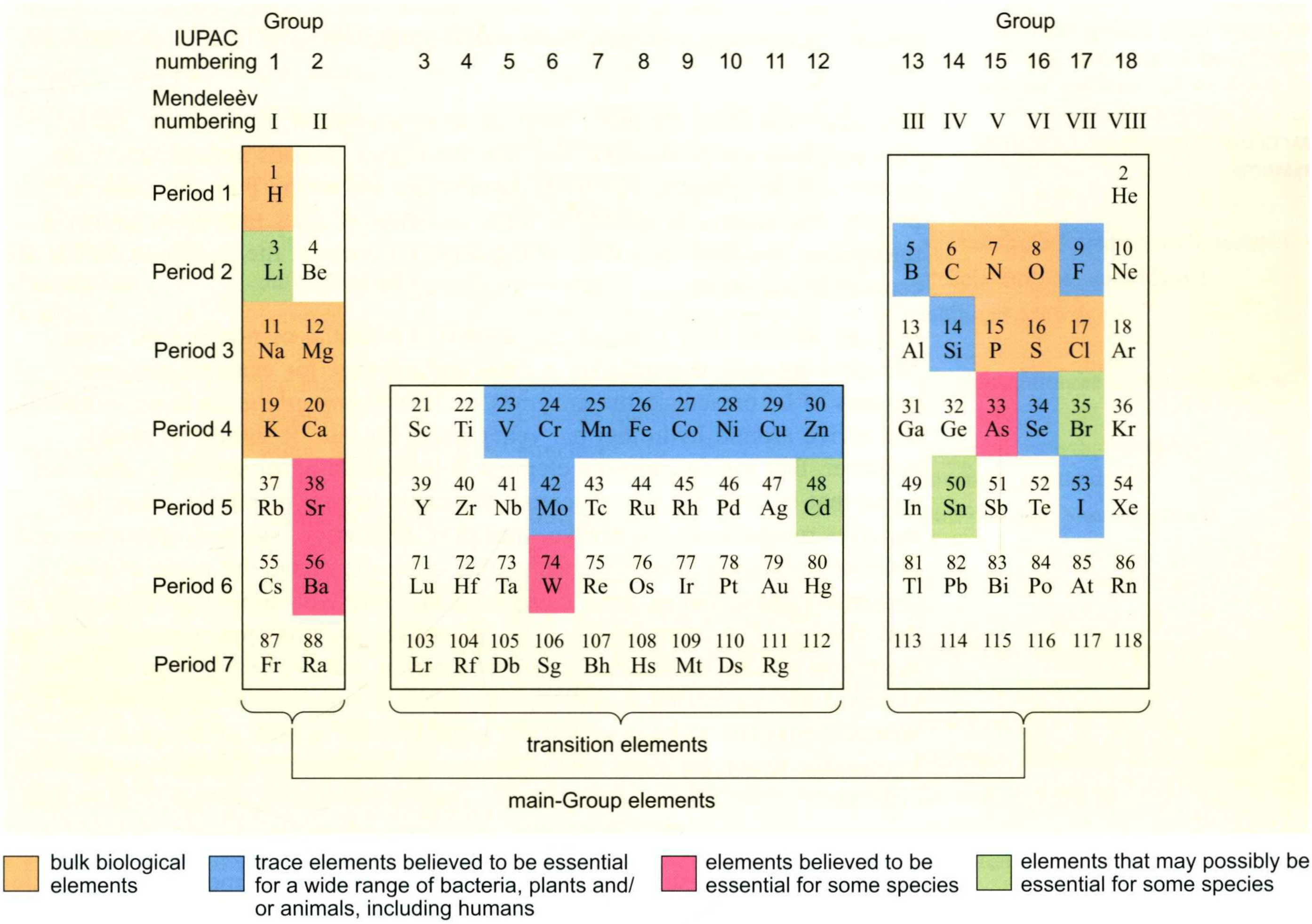

Figure 1.1 Biological Periodic Table of the elements. Elements that occur naturally and are essential for many biological systems are highlighted in blue; those believed to be essential or possibly essential for at least one species are shown in pink and green, respectively. Bulk biological elements are shown in orange.

The bulk organic elements, carbon, hydrogen and oxygen, together with nitrogen, make up 99% of the human body (shown in Table 1.1). In particular, the high percentage of hydrogen and oxygen reflects the high water content present in living systems.

Table 1.1 Percentage of atoms in the human body.

Element	Atom/%
hydrogen	62.8
oxygen	25.4
carbon	9.4
nitrogen	1.4
other	1.0

The field of bioinorganic chemistry as a research area is relatively new, having become established in only the past 50 years or so, focusing on the role of inorganic elements, particularly metals, in biological systems.

The term '**bioinorganic**', which is a composite of biology and inorganic, is used to describe the occurrence and properties of inorganic elements in living systems. Excluding nitrogen, these make up the 1.0% of 'other' elements in Table 1.1.

It is clear that these elements occur in most groups of the Periodic Table, although they are predominantly from the higher Periods and include both metals and non-metals. The wide distribution across the Periodic Table is perhaps not surprising given the wide variation of roles that these elements undertake. You may note that, as a group of elements, the transition metals are especially important.

It is not always clear whether an element is essential or not; indeed some elements are only essential for a particular species, for example tungsten appears to be present in the enzymes of *hyperthermophilic archaea*, organisms that thrive around hydrothermal vents under the sea. It should be noted however, that just because an element is present in an organism, it does not mean that it is necessarily essential. Nutrients have a metabolic route that involves mechanisms for uptake, transport, regulation, storage, utilisation and ultimately disposal. Some elements may enter the metabolic route of another (essential) metal and in some cases may interfere with biological processes of that element. For example, the average human contains approximately 300 mg strontium which chemically resembles calcium, but is not believed to be essential for our health; it is also, fortunately for us, not toxic. (Strontium is however believed to be essential for some corals.) A lack of detailed knowledge about the exact role of each element can make classification difficult.

In this book we will explore different roles that metal ions play in biological systems. We will first look at the diverse functions that some of the inorganic elements in the biological Periodic Table undertake in humans. Many of these elements will also be essential for other animals, plant life and bacteria, and although there will be some commonality, the exact functions understandably will differ in many cases.

1.1 Essential inorganic elements for human life

Table 1.2 shows the typical mass of some of the essential bioinorganic elements in a 70 kg human (collectively included as the 'other' elements in Table 1.1), together with their biological functions. Serious disorders (also listed in Table 1.2) may result from their deficiency (or indeed overload). By studying these elements in a biological context, not only can we learn what roles they play in biology, but also we can provide a foundation for understanding, and eventually treating, many of the health problems listed. The major dietary source of each element is also included.

Table 1.2 Mass and dietary sources of bioinorganic elements in a typical 70 kg human, and the functions that they undertake.

Metal	Mass/g	Dietary source	Function	Effect of deficiency
calcium	980	dairy, vegetables, sardines	structure, charge carrier	retarded skeletal growth
phosphorus	770	fish, meat, eggs, dairy	structure, ATP	
sulfur	140	fish, meat	amino acids	
potassium	140	fruit, nuts	charge transfer, regulation of intracellular fluid	*
sodium	98	cereals, salt	charge transfer, regulation of intracellular fluid	*
chlorine	84	salt	utilisation of glucose	mild diabetes*, reduced cholesterol
magnesium	19	nuts, chocolate	structure	muscle cramps, convulsions
silicon	18	cereal	unclear†, possibly present in connective tissue	inhibited growth
iron	4	red meat, fortified cereals	oxygen transport and storage, electron transfer	anaemia, immune system disorders
fluorine	2.6	water, meat, egg, tea, dairy	structure	inhibited growth, infertility, anaemia, dental decay
zinc	2.3	red meat, cheese, herrings	structure, enzyme	skin damage, stunted growth
copper	0.07	seafood, meat, nuts	component of many enzymes (e.g. cytochrome c oxidase)	anaemia, artery weakness
manganese	0.014	cereal products, nuts	enzyme, glucose metabolism	infertility, inhibited growth
molybdenum	0.007	meat, egg, beans	enzyme	poor cell growth
nickel	0.007	vegetables, pulses	enzyme	inhibited growth
selenium	0.0035	cereal, bread	enzyme	anaemia, infertility
chromium	0.0021	wheatgerm, kidney	unknown†, possible involvement in glucose tolerance	diabetes symptoms
vanadium	0.0021	seafood, liver	regulates enzyme	inhibited growth
cobalt	0.0014	vitamin B_{12}, sardines, egg, liver	component of vitamin B_{12} (cobalamin)	pernicious anaemia
iodine	0.0014	milk, fish	regulates metabolic function (temperature)	goitre (swollen neck due to enlarged thyroid), retarded metabolism

* Sodium, chlorine and potassium deficiency is rare, and acute cases only tend to occur with severe dehydration.

† Role is not certain.

These elements can crudely be classified into either bulk or trace elements. A bulk element makes up a significant percentage by mass of most organisms (>0.1%), whereas a trace element is present in most organisms in only very small quantities.

Table 1.2 shows three clear classes of elements. The bulk metals, calcium, potassium, sodium and magnesium form one class, and together with the other bulk elements, phosphorus, sulfur, chlorine and silicon, make up just less than 1% of the atoms in the body. These elements (mostly in ionic form) occur widely throughout the body and indeed are essential for *all* life. Calcium and phosphorus (as phosphate), are particularly abundant in animals, owing to their presence in bone. Calcium is also found in a variety of proteins and enzymes, and together with sodium and potassium, it is important for signal transmission in nerves. Sulfur (and the other bulk inorganic element, nitrogen) is present in amino acids and proteins.

A second class of elements contains the trace elements including iron, fluorine, zinc and copper, which are found in small quantities and are required by most biological systems. Both iron and zinc ions are found in blood proteins, and are also components of a large number of enzymes, as is copper. Fluorine is found in bone and teeth, and is added to drinking water and toothpaste to help prevent corrosion of tooth enamel.

A third class contains elements that are found in very small amounts and includes the trace metals manganese, chromium, molybdenum, cobalt and vanadium. These are sometimes referred to as 'ultra trace' elements and in common with the other essential transition metals discussed above are often important components in enzymes.

■ How do humans maintain adequate levels of these inorganic elements in our bodies?

□ We acquire these elements from the food and water that we consume. A list of dietary sources is given in column 3 of Table 1.2.

Of the inorganic elements, it is the important role that metals in particular play in life that will form the basis of this book. We will briefly consider some of the key functional roles that metals undertake in biological proteins in the next section. But first you should note that other than the alkali and alkaline earth metals, most metals in biological systems are associated or coordinated with ligands as **coordination compounds** or **complexes**. In Chapter 2, we will consider three major classes of 'biological' or 'biochemical' ligands that bind with metals: peptides or proteins with suitable amino acid side chains, macrocyclic ligands, such as porphyrins, and finally, the nucleobases found in DNA. The ability of the transition metals to form coordination compounds is also important in the mechanisms involved in the acquisition, transport and storage of metals as we will see in Chapters 3–5 of this book.

1.2 Functional roles of metals

As you saw in Table 1.2, many biological processes involve metals. Metals play a role at a number of different levels as illustrated in some key examples below. In many of these examples the metals are constituents of proteins, forming a group of proteins called **metalloproteins**. The metal ions, commonly described as 'metal cofactors', can help to perform physiological functions. The metal can be present as a single ion, a pair of ions or as a cluster.

Let's start, at the molecular level, with perhaps one of the most well-known examples of a metal in living systems, iron. Iron is required by almost all organisms and has an essential role to play in many enzymes and proteins. In mammals, including humans, iron is an integral part of the blood; a deficiency leads to anaemia, a condition that affects many people. Accordingly, the bioinorganic chemistry of iron has been studied extensively, with many studies concentrating on the blood protein **haemoglobin**, which is an oxygen-carrier in the blood. The iron centre of haemoglobin, called **haem**, shown in Figure 1.2a, provides a site to which the oxygen molecule can bind. The iron in haem, acts as a **Lewis acid**, accepting a non-bonding or lone pair of electrons from the oxygen. This binding is reversible, allowing transport and delivery of oxygen to where it is required.

You will recall from Figure 1.1 that the transition metals are a particularly important group of bioinorganic elements (many of the trace metals in particular are in this group). One important feature of the transition metals is their ability to exist in more than one oxidation state. Iron, for example, is found typically as either the Fe^{2+} or Fe^{3+} ion. This ability of iron and the other transition metals to exist in variable oxidation states is at the root of their ability to function as **electron transfer agents**, transferring electrons to enzymes to perform a specific function. One example is the 4Fe–4S cluster of ferredoxin illustrated in Figure 1.2b, important in bacteria for nitrogen fixation, which can take an overall charge of −3, −2 or −1 depending on the charge on the iron.

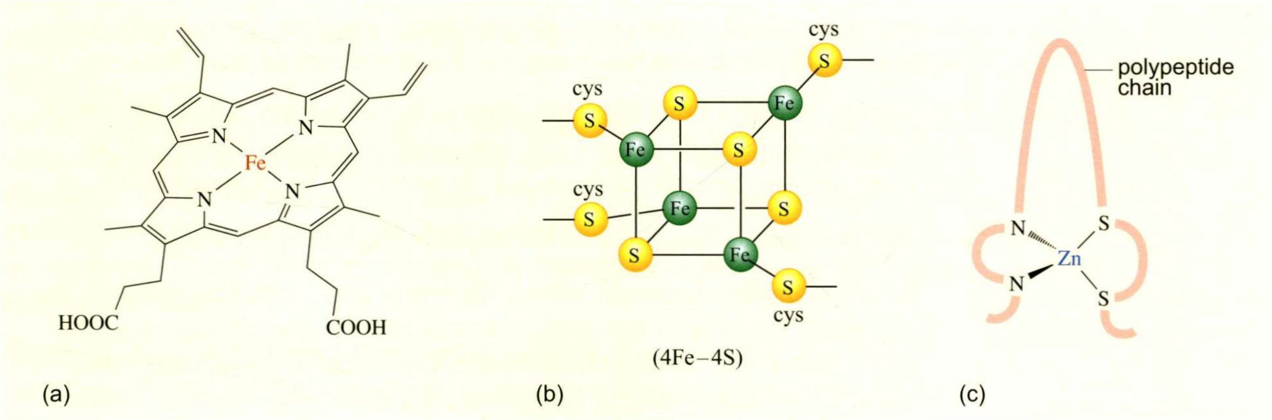

Figure 1.2 Structure of (a) haem, (b) 4Fe–4S cluster in ferredoxin and (c) Zn finger. Cys is the amino acid cysteine.

Metal ions may also be incorporated (deeply buried) into metalloproteins in a structural role. An example is that of Zn^{2+} metal ions which are found in many proteins, including 'zinc-finger proteins' (Figure 1.2c) which recognise and bind to particular sequences of DNA (deoxyribonucleic acid) and are important in transcription. The Zn^{2+} ion is believed to be essential in maintaining the protein's three-dimensional structure. On genetic evidence, it has been suggested that there may be up to 200 zinc-finger proteins waiting to be characterised.

Metals are also present in a subclass of metalloproteins, called **metalloenzymes**. (Enzymes are proteins that act as biological catalysts.) Many of the physiological reactions important in life are catalysed by metalloenzymes. Examples include the catalytic reduction of O_2 to water (important in respiration) and the reduction of nitrogen to ammonia (important in nitrogen fixation in certain groups of bacteria). In these metalloenzymes the metal ion may be part of the catalytic active site itself or used to transfer atoms or groups to the active site.

Note that the relationship between the metal and protein can work in two ways. The presence of the metal can influence the electronic and structural features of the protein. The protein can also influence the properties of the metal, for example by stabilising unusual coordination geometries or particular oxidation states. The complex interplay between these two aspects will determine the reactivity in the system. We will come across many examples of this throughout the book.

Metal ions can also have a role on their own as counter ions. For example Mg^{2+} ions have a structural role, stabilising the DNA double helix by binding the phosphate groups so preventing the strands from repelling each other.

At the cellular level, metals ions, in particular the alkali and alkaline-earth metal ions Na^+, K^+ and Ca^{2+}, are used in biology in communication roles to trigger cellular response. For example, a rapid influx of Na^+ ions into a cell triggers the firing of neurons in nerves.

Solid calcium compounds also play a structural role at the macroscopic level, as a major component in bone, teeth and shell. Metal ions, in particular iron in magnetite, Fe_3O_4, may be used by some organisms as internal magnetic compasses by which to navigate. Magnetotactic bacteria, for example, use magnetite to orient themselves along the Earth's magnetic field lines.

This section is just a brief taster of some of the chemistry which influences the functions that metals can play in biological processes. These will be developed further throughout this book, in particular in Chapters 6–8.

■ List the various functions of the metal in the examples above.

□ In the examples discussed above, the metal ions in metalloproteins are important for oxygen transport, electron transfer and also in structural roles. Metal ions are also important components of metalloenzymes, either at the active site, or responsible for delivering reactants to the active site. Metal ions can also have a communication role, and may also provide structure at a macroscopic level, in bone, for example.

- ■ What key properties do transition metals display that are utilised in metalloproteins?
- □ The two key properties, illustrated in the examples above, are the ability of transition metals to occur in different oxidation states and also the Lewis acid behaviour of metals.

Finally, before moving on you should note that, in addition to these naturally occurring inorganic elements, metals are also introduced into biological systems for medicinal use with widespread application in both diagnostics and therapy (Table 1.3). Examples such as these will be considered in the online chapter (Chapter 9) of this book.

Table 1.3 Examples of metals used in medicine and their application.

Metal	Medicinal use
Pt, Ru	therapy: anticancer therapy
Ba	diagnostic: Ba meals in X-ray
Gd	diagnostic: MRI contrast agent
Tc	diagnostic: radiopharmaceutical for functional imaging
Re	therapy: radionuclide for therapy
Au	therapy: arthritic drug
V	therapy: diabetes (insulin mimic)
Bi	therapy: treatment for peptic ulcers
Li	therapy: drug for bipolar disorders

1.3 Bioavailability of metals

As you have already seen, certain metals are essential for life. Remarkably, there is very little variation in the relative proportion of the elements from one person to another. Indeed, any significant variation can lead to disease.

One question we might ask is why has an organism chosen one specific element rather than another. A major factor will be the chemical suitability of the element for a particular function, as we have seen briefly in the previous section, but it will also depend on their availability (both now and in the past).

For an element to be of use to an organism, it must be 'available' in the local environment of the organism. This will depend on two factors. First, the abundance of the element will be important. Second, the element must be in an accessible or extractable form such that it can be taken up or acquired by an organism. This availability of metals to biological organisms is referred to as **bioavailability**.

Although we acquire most of our metal nutrients from our diet, this will ultimately depend on the absorption of these nutrients by plants from the soil. The abundance of the different metals in the Earth's crust is shown in Table 1.4. Almost all metals occur as oxide, carbonate or sulfide ores, as shown in column 3 of the table.

Table 1.4 Elemental composition of the Earth's crust and seawater for the essential metals.

Element	Earth's crust/ppm	Major ores	Seawater/ppm
Ca	5×10^4	$CaCO_3$, $CaMg(CO_3)_2$, $CaSO_4.2H_2O$, CaF_2	4×10^2
Co	30	CoS_2, CoAsS, $CoAs_2$, Co_3S_4	$< 1 \times 10^{-4}$
Cu	68	$CuFeS_2$	3×10^{-3}
Fe	6×10^4	Fe_3O_4, Fe_2O_3, FeO(OH)	3×10^{-3}
K	1.5×10^4	KCl	416
Mg	3×10^4	$CaMg(CO_3)_2$, $MgCO_3$	1.3×10^3
Mn	1×10^3	$MnCO_3$, MnO_2, MnO(OH)	2×10^{-3}
Mo	1.1	MoS_2	0.01
Na	2.3×10^4	NaCl, $Na_3(CO_3)(HCO_3)$	1.1×10^4
Ni	90	$(Fe,Ni)_9S_8$	2×10^{-3}
V	190	$K(UO_2)(VO_4).1.5H_2O$, $PbCl_2.3Pb_3(VO_4)_2$	1.5×10^{-3}
Zn	79	ZnS	5×10^{-3}

■ According to Table 1.4, which are the two most abundant essential metals in the Earths crust?

□ Calcium and iron appear to be the most abundant metals. As we will see in the next section, the abundance of a metal in the Earth's crust however does not necessarily reflect its true availability.

1.3.1 Aqueous chemistry

Much of the chemistry of life occurs in aqueous media, highlighted by the high water content of organisms (emphasised by the percentages of H and O in the human body in Table 1.1). Most of the metals in our diet are in the form of water-soluble salts. Thus the solubility of metals is an important factor to consider. Solubility will depend on the nature of the metal salt, and also on the pH and temperature of the solution. Human life is restricted to a narrow range of conditions, generally a pH of 7 and a temperature of 303 K.

As the concentrations of metals in solution are likely to be more important generally than the amount of an element present in rocks (i.e. solid compounds), we are justified in considering that the availability of elements may be better reflected if we consider the abundance of the elements in the oceans, shown in Table 1.4 (column 4). When we compare the abundance of the elements in the oceans with their overall abundance in the Earth's crust, quite a different pattern emerges.

For example, the iron content of the Earth's continental crust is actually relatively high (4.1%), but most of it exists as the highly insoluble – and, therefore, unassimilable (not able to be incorporated into) – compounds, hydrated iron oxide (hematite), $Fe_2O_3.nH_2O$, iron hydroxide, $Fe(OH)_3$, magnetite, Fe_3O_4, or siderite, $FeCO_3$. This is reflected in the low concentration of iron in seawater. This however has not always been the case (Box 1.1).

