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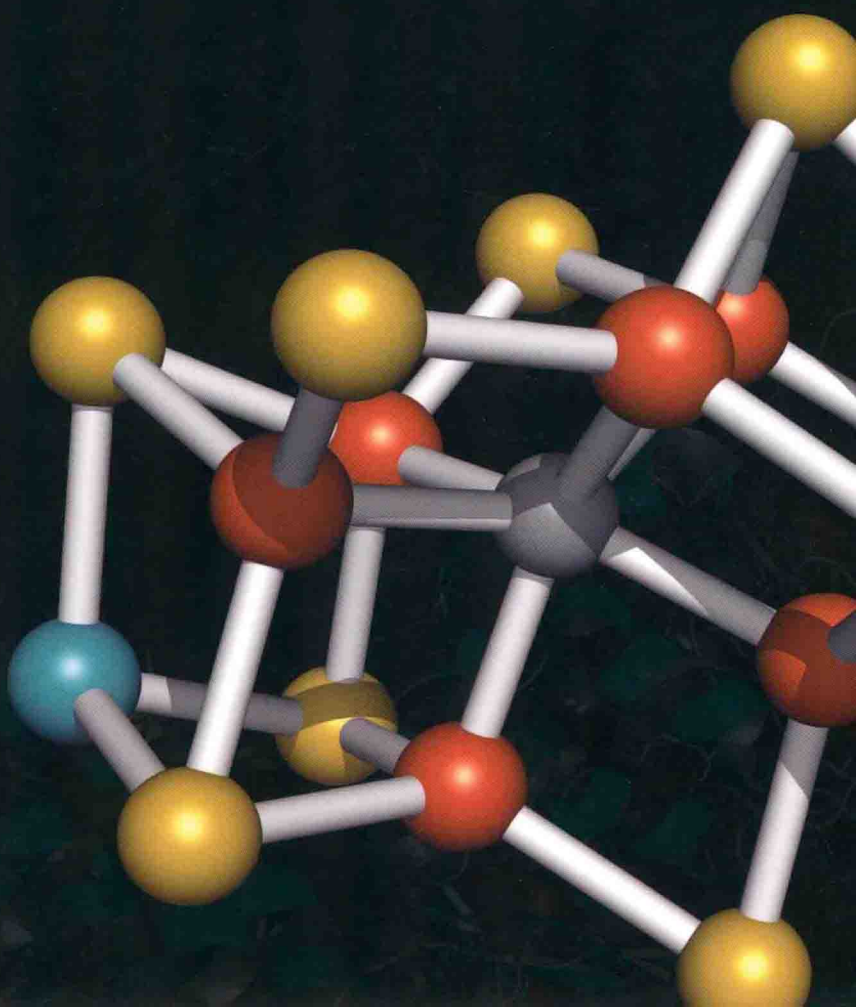
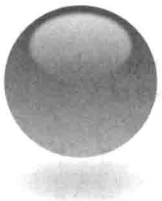
BIOINORGANIC CHEMISTRY





Bioinorganic Chemistry

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Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
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British Library Cataloguing in Publication Data
Data available

Library of Congress Control Number: 2013948265

ISBN 978-0-19-965519-9

Printed in Great Britain by

Ashford Colour Press Ltd, Gosport, Hampshire

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Introduction

Bioinorganic chemistry explores the role of 'inorganics' in biological and biomimetic processes. Inorganics are metal ions and metal compounds of variable complexity: anions and cations such as sulfate, phosphate, and the ammonium ion; and neutral molecules involved in biological processes such as dioxygen and ozone, and the oxides of carbon, nitrogen, and sulfur. All of these inorganic ions and molecules can play an intrinsic role in a range of physiological functions. They are therefore essential for sustaining life—as long as homeostasis is not disrupted. Conversely, the dysfunction of life processes can be attributed to an undersupply or oversupply of inorganics, either through malnutrition or as a result of disturbances caused by genetic and/or effects related to environmental and dietary imbalance, or illness.

An estimated one-third of the proteins, and one-half of all enzymes, which collectively perform a variety of tasks, contain metal ions. Many of these enzymatic processes concern redox reactions on the one hand, and processes involving the making and breaking of bonds in respect to the formation and disruption of organic (and inorganic) molecules by non-redox processes on the other. Esterification and hydrolysis are typical reactions in this respect. In order for metal ions to become resorbed, to 'locate' their target molecules, and to be desorbed, organisms require suitable recognition and transport systems—transport systems that have available coordination sites that match the metal ion and its oxidation state.

Life processes involve (i) metabolism—the chemical transformation of matter coupled with energy production or consumption, (ii) replication/reproduction (coupled to the storage and transfer of information), and (iii) evolutionary modulation—the optimization of the chances of survival in a given habitat and the adjustment to changing environmental conditions. Evolutionary adaption is achieved by mutation within the individual gene pool, and by horizontal gene transfer between different (bacterial) species.

Inorganic processes, intrinsically linked to biochemical reactions, participate at all these levels. In this context, during this book we also focus on environmental and medicinal concerns. Examples of 'inorganics' in medicine include: the treatment of certain types of cancer with platinum prescriptions; and the use of paramagnetic gadolinium and radioactive technetium compounds in diagnosis.

The present book arises from a lecture course called 'Bioinorganic Chemistry', delivered by the author during the past two decades at the University of Hamburg, Germany, and, in 2008, at the University of Lund, Sweden. The idea for the book was initiated by Ebbe Nordlander, Lund University, who also had been involved in developing the original concept of this book.

Structuring the wealth of material has been a particularly challenging task. For an inorganic chemist, it is tempting to arrange the material according to elements. In biology, however, the focus is often on function. A combination of these two approaches has been pursued in the present book: elements that have a pivotal role in (almost) all biological functions (alkaline and alkaline earth metals, iron, zinc, and sulfur) are addressed in separate chapters, while other chapters are dedicated to functional processes. Examples of the latter are oxidoreductases, enzymes of the nitrogen cycle, and photosynthesis, while the general role of nickel is

covered in the context of methanogenic/methanotrophic prokarya. Two extra chapters are dedicated to the metal–carbon bond and to inorganics in medicine, respectively.

The book is written for students with a basic knowledge of general, inorganic, and organic chemistry (plus basics in biochemistry), including analytical methods. Irrespective of this general caveat, introductory chapters provide a general review of the bio-elements (Chapter 1) and 'Life' (Chapter 2). Additional supporting information is provided in sidebars, which are distributed throughout the book. These briefings encompass analytical methods frequently employed for the characterization of bioinorganic species, overviews of concepts (such as symmetry and radioactivity), and overviews of functional regimes, for example copper enzymes and organic redox systems.

Finally, I would like to thank Jonathan Crowe from Oxford University Press for his constructive comments in the process of the final shaping of the book chapters.

Dieter Rehder
Hamburg, June 2013

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Contents

List of sidebars

1 Bio-elements in the periodic table

In this introductory chapter, we will provide a brief overview of those chemical elements that have biological and medicinal functions. For the latter, we will consider metals that have a direct impact on physiological activity; metals employed, for example, in supports or as substitutes for joints (such as titanium alloys) are thus excluded. On the other hand, we include toxic compounds based on mercury, lead, and arsenic. In the second part of the chapter, we provide overview of the main ligands and ligand functions available for metal ions in biological systems. The term 'metal ion' is used here in a broader sense, including metalloids (such as Si, As, Sb, and Se). Ligands do not only mediate the transport and storage of metal ions, but also fine-tune the metal's physiological actions.

In the periodic table of the bio-elements in Fig. 1.1, elements of biological relevance are classified according to four categories. The elements C, H, O, N, and S (in black) account for the main part of organic matter and thus for 'biomass'. In addition, many elements commonly considered 'inorganic' play an important role in a biological and, more specifically, physiological context. Some of these elements, in light grey, are present in (almost) all organisms. The alkaline metals Na and K, the alkaline earth metals Mg and Ca, the transition metals Mn, Fe, Co, Cu, and Zn, and the non-metals P, Se, F, Cl, and I belong to this category. Other elements, shown in dark grey (the metals V, W, Ni, and Cd, the half-metal Si, and the non-metal B) are important in a restricted number of organisms only.

Elements shown in dark blue in Fig. 1.1 are used in medicinal therapy or diagnosis (see Sections 14.3 and 14.4), and may thus be classified as medicinal elements. There are additional elements that affect living organisms either by their direct toxicity in very low doses and/or by their destructive radioactive potential. Of the toxic elements, we explore As, Pb, and Hg (in light blue) in Section 13.2. Toxic effects exerted by overloads of otherwise beneficial elements, in particular Fe and Cu, shall be considered in the respective chapters dedicated to these elements and their functions.

Specific chapters providing surveys on single elements or groups of elements are dedicated to the alkaline and alkaline earth metals (Chapter 3), iron (Chapter 4), and zinc (Chapter 12). The nitrogen and sulfur cycles are discussed in some detail in Chapter 8 (sulfur) and Chapter 9 (nitrogen), respectively.

For elements highlighted in blue and grey shades in Fig. 1.1, we provide a brief summary of their main biological function and/or medicinal application in the following pages, including, where appropriate, links to the respective chapter, section, or sidebar. The numbering of sidebars matches the numbering of chapters. For elements primarily present as free ions or in ionic compounds, the charge is denoted in Arabic numerals (such as Mg^{2+}); for elements chiefly present in covalent compounds, Roman numerals are utilized—for example,

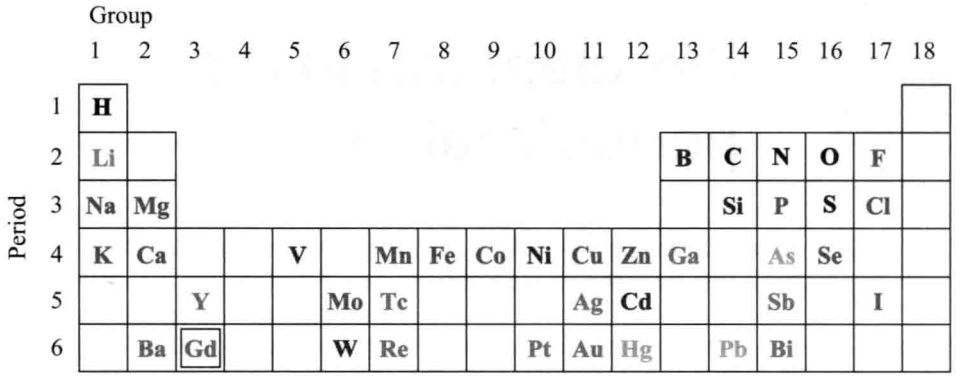

Figure 1.1 Periodic table of the bio-elements. Black: elements which build up biomass; light grey: additional generally essential elements; dark grey: essential for some groups of organisms only; dark blue: medicinally important elements (in therapy and/or diagnosis); light blue: elements addressed in the context of their toxicity. Gadolinium (Gd) is framed because it is a member of the lanthanoid subfamily.

Fe^{II} and Se^{-II}. Boron and silicon are included in this overview, including key references, but not treated in extra chapters.

Li^+ is used in the treatment of bipolar disorder (manic depression) and hypertension (14.3.4).

Na^+ and K^+ are the most important 'free' intra- and extracellular cations. They are responsible for, for example, the regulation of the osmotic pressure, membrane potentials, enzyme activity, and signalling (3.3).

Mg^{2+} is the central metal ion in chlorophyll (11.2). Mg is further involved in anaerobic energy metabolism (adenosine triphosphate → adenosine diphosphate + inorganic phosphate), and the activation of kinases and phosphatases (3.4), and thus triggers activation paths.

Ca^{2+} plays a pivotal role in signalling, muscle contraction, and enzyme regulation (3.5). Ca^{2+} can be a cofactor in hydrolases, and can play a role in determining the structure of biological molecules, for example in thermolysin (12.2.2). Ca is also constituent of the photosynthetic oxygen-evolving centre (11.2), and plays a role as a second messenger and in the activation of enzymes (3.5). Calcium, in the form of partially fluorinated hydroxyapatite $Ca_5(PO_4)_3(OH,F)$, is the main inorganic part of the endoskeletons (bones, teeth, enamel) of vertebrates (3.5). Exoskeletons of, for example, mussels, shells, corals, and sea urchins are built up of aragonite and calcite, $CaCO_3$ (3.5).

Gd^{III} is the most common paramagnetic metal centre in contrast agents in magnetic resonance imaging (14.4).

$V^{III/IV/V}$ constitutes the active centre of vanadate-dependent haloperoxidases (7.2) and vanadium nitrogenase (9.1). V^{3+} and VO^{2+} are accumulated by ascidians, V^{IV} (in the form of amavadin) by *Amanita* mushrooms (7.2).

$Mo^{IV/VI}$ is constituent of molybdo-pyranopterins, and thus in a component of the active centre of a variety of oxidoreductases and in acetylene hydratase (7.1). Molybdenum is further a constituent of the FeMo-cofactor in molybdenum-nitrogenases (9.1).

$W^{IV/VI}$-based tungsto-pyranopterins (analogues of the corresponding molybdenum cofactors) are present in several oxidoreductases, mainly of thermophilic archaea (7.1).

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$Mn^{II/III/IV}$ constitutes the basis of the $\{CaMn_4O_5\}$ cluster of the oxygen evolving complex in photosynthetic water oxidation (11.2). Ribonucleotide reductases can contain one or two Mn centres (6.1), and Mn can also be the active metal ion in superoxide dismutases (6.2).

^{99m}Tc is a metastable γ-emitter ($t_{1/2}$=6 h). Its coordination compounds are employed in radio diagnostics of, for example, bone cancer and infarct risk (14.4).

$Fe^{II/III/(IV/V)}$: this multi-functional and omnipresent element is stored and 'operated' by proteins (ferritins, Dps proteins, and frataxins) (4.2). Bio-mineralization of iron compounds leads to the minerals ferrihydrite, goethite, magnetite, and greigite (4.2). The transport protein transferrin (4.2) regulates iron transport; pathological dysfunction can cause iron overload and deficiency (14.2.1). Biological functions mediated by iron include the oxygen transport by haemoglobin (5.1) and haemerythrin (5.2), and electron transfer (redox) reactions. Fe-based electron transfer proteins can depend on iron–sulfur clusters (9.2, sidebar 5.1), haem-type iron (Chapter 5), and dinuclear and mononuclear non-sulfur and non-haem iron proteins (Chapter 6). Additional examples of iron-based enzymes are the oxygenase P_{450} (6.3), methane monooxygenase (10.3), ribonucleotide reductase (7.1), iron-only hydrogenases (10.2), and NO reductase (9.2). Carbonyl and cyano complexes of iron play a role in nickel–iron and iron-only hydrogenases (13.1).

$Co^{I,II,III}$ is the central ion in synthases and isomerases of the cobalamine family. An example is vitamin B_{12} (13.1), the methyl form of which is also employed in the methylation of organic and inorganic substrates, for example in the context of methanogenesis (10.2).

$Ni^{I/II/III}$ is a main metal in methanogenesis, where a NiFe hydrogenase and the so-called factor F_{430} with an interim Ni–CH_3 centre (10.2) are active. Carbonyl–nickel intermediates are formed in the course of the activities of NiFe-CO-dehydrogenase and acetyl coenzyme-A synthase (13.1). Additional examples of processes catalysed by Ni-dependent enzymes include the hydrolysis of urea and the dismutation of superoxide (10.4).

$Pt^{II/IV}$-based complexes are used in the chemotherapy of cancer (mainly of the ovaria and testes). A prominent example is cisplatin *cis*-$[Pt(NH_3)_2Cl_2]$ (14.3.3).

$Cu^{I/II}$ mediates oxygen transport by haemocyanin (5.2). Active centres containing 1–7 Cu ions are involved in electron transport enzymes such as plastocyanin (11.2), nitrite and NO reductases (9.3), catechol oxidase and galactose oxidase (6.3), and in oxygenases (tyrosinase) and dismutases (6.3). Copper possibly also plays an active role in Alzheimer's disease (14.2.2).

$Au^{I/III}$ compounds are considered in the context of the treatment of arthritis (14.3.2).

Zn^{2+} is in the active centre of enzymes including hydrolases, carboanhydrase, and alcohol dehydrogenase (12.2). Other zinc dependent functions are manifest in genetic transcription (zinc fingers), in the stabilization of tertiary and quaternary structures of peptides (12.3), and in DNA repair proteins (12.3). Low molecular mass proteins rich in zinc, so-called thioneins, store zinc and regulate zinc levels, but can also act as scavengers for toxic Cd^{2+} and Hg^{2+} (12.4).

Cd^{2+} is a zinc antagonist and therefore toxic, because it binds more effectively to cysteinate residues and thus inhibits the activity of zinc enzymes. By way of exception, Cd^{2+} can replace Zn^{2+} in the carboanhydrase of marine diatoms (12.2.1).

$Hg^{I/II}$: mercurous (Hg_2^{2+}) and mercuric (Hg^{2+}) compounds are particularly toxic because they denature proteins by the formation of insoluble HgS or HgSe when reacting with cystine and cysteine, or selenocysteine. In mammals, Hg^{2+} is metabolized to methylmercury, CH_3Hg^+ (13.2.1).

B^{III} is a constituent of a few naturally occurring antibiotics (such as boromycin). In the form of borate, it can be employed as a stabilizing component of herbal cell walls (see also [1]).

Si^{IV}, in the form of silicates, is involved in the build-up of bones. Silica (SiO_2) and silicagels ($SiO_2 \cdot xH_2O$) are employed as a stabilizing support in monocotyledonous plants (such as grass) and *Equisetum*, and constitute the shells of diatoms (→ kieselgur). Dietary silicon is likely beneficial to bone and connective tissue health [2].

P^{V} in phosphates, ($H_nPO_4^{(3-n)-}$), is a constituent in hydroxy- and fluorapatite $Ca_5(PO_4)_3(OH/F)$ of the bone and enamel. Esters of mono-, di- and triphosphate are further involved in energy metabolism (ATP/ADP/AMP, *c*-GMP), in the activation of reductants such as NADPH (sidebar 12.1), and in the activation of organic substrates in metabolic and catabolic pathways. Phospholipids—lipids containing a phosphoester unit—in cell membranes, and other phosphate esters, including DNA and RNA, are indispensable and thus common in all organisms.

$As^{III/V}$: toxic As_2O_3 (arsenic) is metabolized to methyl arsenates (13.2.4); arsenate ($HAsO_4^{2-}$) is a life-threatening antagonist for phosphate.

Sb^{III}, for example in the form of Sb_2O_3 or Sb_2S_3, has sporadically been utilized as a 'disinfectant', for example in the treatment of inflammatory skin pimples such as acne (14.3.1). Antimony compounds are toxic.

Bi^{III}-based prescriptions are used in the treatment of gastritis (14.3.4) such as caused by *Helicobacter pylori*.

Se^{-II} is the key constituent in selenocysteine, an essential amino acid present in specific enzymes, for example in glutathione peroxidase, and in some representatives of the molybdopterin cofactor of oxidoreductases (7.1).

F^- (fluoride) partly replaces OH in apatite (3.5). The teeth of sharks are almost completely fluorapatite $Ca_5(PO_4)_3F$.

Cl^- is, along with hydrogencarbonate, the most important free anion in physiological liquids (Table 14.1). Its functions range from the regulation of ion homeostasis to the regulation of electrical excitability [3].

I^- is an essential constituent of thyroid hormones such as thyroxin. These hormones stimulate diverse metabolic activities in tissues, and are also involved in genetic transcription [3].

The cations of transition metals are commonly not present in a free form, but are rather coordinated to (complexed by) ligands. In particular, this applies to metal ions in the active centres of enzymes, or else integrated into peptides and proteins, mostly as structure stabilizing factors. Representative ligands are listed in Fig. 1.2: **N**-functional ligands can be provided by the amide linkage of the peptide moiety, by porphinogens, histidine Nδ or Nε, lysine and arginine; **O**-functional ligands by the peptide amide, tyrosinate, serinate, glutamate, and aspartate; **S**-functional ligands by cysteinate and methionine, and the **Se**-function by selenocysteinate. O, S, and Se can also be present as doubly bonded, dianionic ligands (oxido, sulfide and selenido ligand), or as singly bonded OH^-, SH^-, and SeH^-. In addition to the organic peptide/protein and haem-type ligands, simple inorganic ligands are also often employed; see row (5) in Fig. 1.2.

Ligands coordinating via sulfur, such as cysteinate and sulfide, are classified as soft (in the sense of deformable) ligands, ligands coordinating via oxygen donors as hard ligands. Nitrogen donors fall in-between. This soft/hard concept goes back to Pearson; see also sidebar 4.1.

Hard metal ions preferentially bind to hard ligands, soft metal ions to soft ligands. There are, however, many exceptions to this simplified generalization. Alkaline and alkaline earth

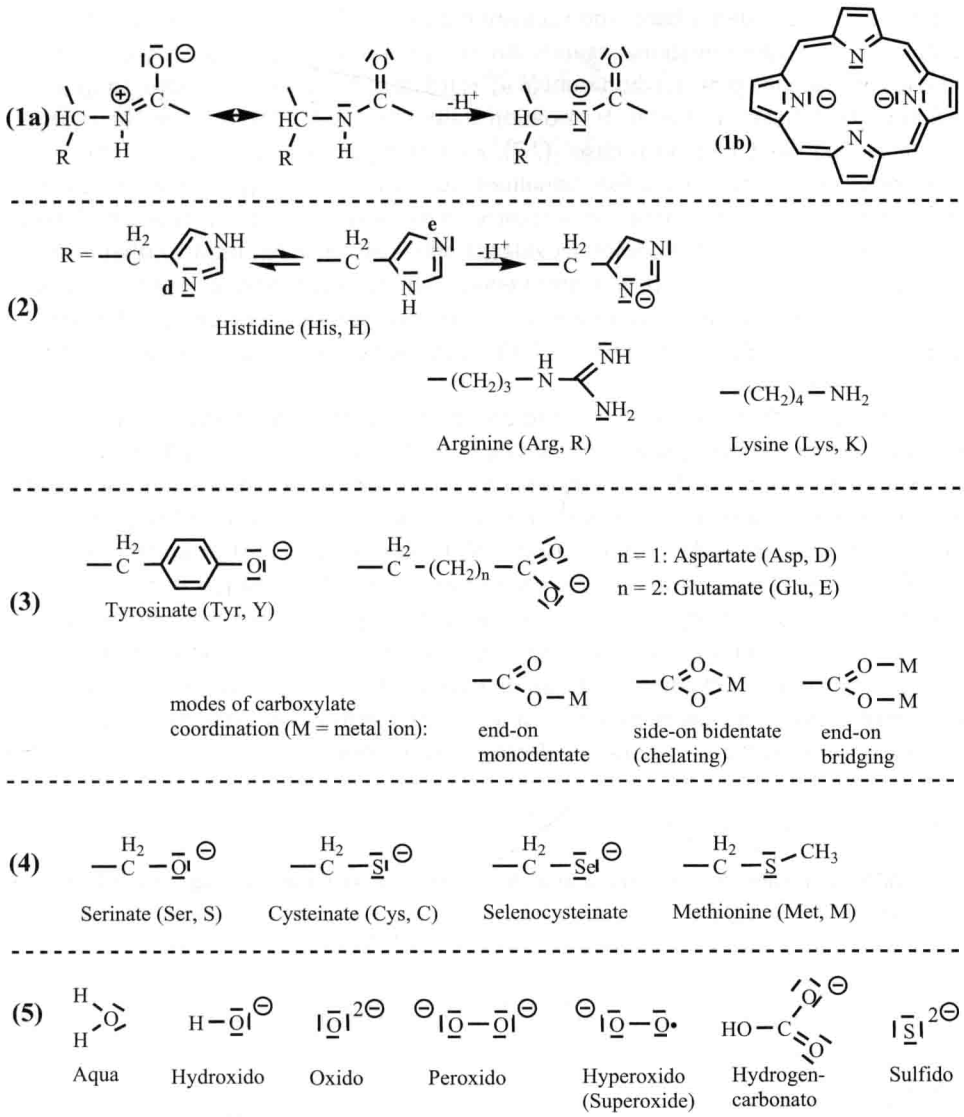

Figure 1.2 A selection of common ligands for (transition) metal ions in biological systems. (**1a**) The peptide function of the protein backbone. Note that the peptide-N can only coordinate out of its deprotonated form, or the neutral mesomeric resonance hybrid, where N is sp^3 hybridized and thus has a free electron pair available. Coordination via the carbonyl-O is also feasible. (**1b**) Porphinogenic ligands, such as the haem-type centre (of cytochromes) shown here, are tetradentate. (**2–4**) Functional groups provided by amino acid residues in peptides and proteins. The three-letter and one-letter codes of the amino acids are given in parentheses. (**5**) Frequently employed inorganic co-ligands.[1]

[1] Note that *ligands* such as O^{2-}, OH^-, O_2^{2-}, and S^{2-} are often termed—not quite correctly—oxo, hydroxo, peroxo, and thio ligands. The nomenclature used throughout this book follows IUPAC recommendations: oxido, hydroxido, peroxido, sulfido, etc.

metal ions are considered hard, and thus are commonly found in a coordination sphere dominated by oxygen-functional ligands. An exception is Mg^{2+} in chlorophyll, where the ion is in a porphyrinogenic environment (3.4). Hard ligands are also commonly targeted by *early* transition metals in their high oxidation states: $V^{IV/V}$, $Mo^{IV/VI}$, $W^{IV/VI}$; see, for example, vanadate-dependent haloperoxidases (7.2), molybdo- and tungsto-pyranopterins (7.1). Manganese also favours oxido functionalities, such as in the oxygen evolving centre in photosynthesis (Chapter 11) where it runs through the oxidation states II, III, and IV. Ferrous (Fe^{II}) and ferric (Fe^{III}) iron, the common oxidation states of iron in nature, are rather unselective: Iron ions bind to hard, soft, and intermediate ligands. Porphinogens readily coordinate Fe, Co, or Ni. Examples are cytochromes (Fe-dependent transporters for O_2 and electrons; Chapter 5), vitamin B_{12} (containing Co; 13.1), and the factor F_{430}, a Ni-based cofactor in methanogenesis; 10.2).

The late transition metal ions $Cu^{+/2+}$ and Zn^{2+} tend to prefer intermediate to soft ligands. Examples of zinc ions exclusively coordinating to thiolate are thioneins (12.4) and the *structural* zinc centre in alcohol dehydrogenase (12.2.3). The *functional* centre in the zinc enzyme alcohol dehydrogenase (12.2.3) exemplifies Zn^{2+} coordination to a mixed N/S ligand set, while in carboanhydrase, the enzyme responsible for the hydration of CO_2 and the dehydration of H_2CO_3 (12.2.1), Zn^{2+} exclusively coordinates to histidines. Mixed thiolate/histidine coordination of $Cu^{+/2+}$ in copper enzymes is exemplified by plastocyanin (in photosynthesis; Chapter 11) or cytochrome-c oxidase, the catalyst in the final step of the electron transfer to O_2 in the respiratory chain (5.3). Nitrite reductase, which contains two functionally coupled copper centres (9.3), is an example for an enzyme harbouring Cu both in an exclusive N-donor environment *and* in a mixed N/S coordination sphere.

Suggested reading

Waldron KJ, Rutherford JC, Ford D, et al. Metalloproteins and metal sensing. *Nature* 2009; 460: 823–830.

The article provides a clue as to how metal sensors in proteins distinguish between different metals and thus select the right metal ion for a specific function, including the delivery of metal ions to functional metalloproteins by metal transporters (metallo-chaperones).

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2 Pre-life and early life forms; extremophiles

Early life forms began to develop on our home planet ca. 3.6 Ga ago (1 Ga = 10^9 years). 'Life' is accompanied by, and depends on, the metabolism of simple and complex organic molecules as well as on inorganics, viz. transition metal ions and non-metals, phosphorus (in the form of phosphate) in particular. The development of protocells from the inventory available in the primordial atmosphere and aquatic sanctuaries, and in minerals present in Earth's crust, as well as the successive evolutionary development of these protocells into primitive bacterial and archaean cellular organisms, took place in an anoxic environment. Successors of these organisms still thrive in niches deprived of oxygen. With the Great Oxygen Event 2.4 Ga ago, probably initiated by photosynthetic cyanobacteria, adaption to an oxic environment became an essential precondition for survival for those unicellular organisms which were no longer confined, or could not retreat to, oxygen-free habitats.

For the more complex organisms (eukarya) evolving ca. two billion years ago (2 Ga), oxygen became *the* element of life—along with environmental conditions (temperature, pressure, pH, atmospheric and aquatic compositions), which we usually term 'normal'. In addition, however, many bacterial and archaean species—but some eukaryan algae as well—have adapted to extremes and are therefore referred to as extremophiles. This includes extremes in temperature, pressure, pH, salt and toxic metal concentrations, resistance towards UV and γ radiation and, of particular interest in the view of bioinorganic chemistry, to carbon sources other than CO_2, electron sources other than (O^{2-} in) water, and energy sources other than light.

In this chapter, we will go back in time to assess briefly the 'chemistry', in the very early days of our home planet, with respect to the scenarios which might have sparked Life. We will then describe the stages of development as the chemical reality and thus the conditions for life to thrive changed through the eons. Finally, adaption to extreme situations, as manifested in extremophiles, will be addressed.

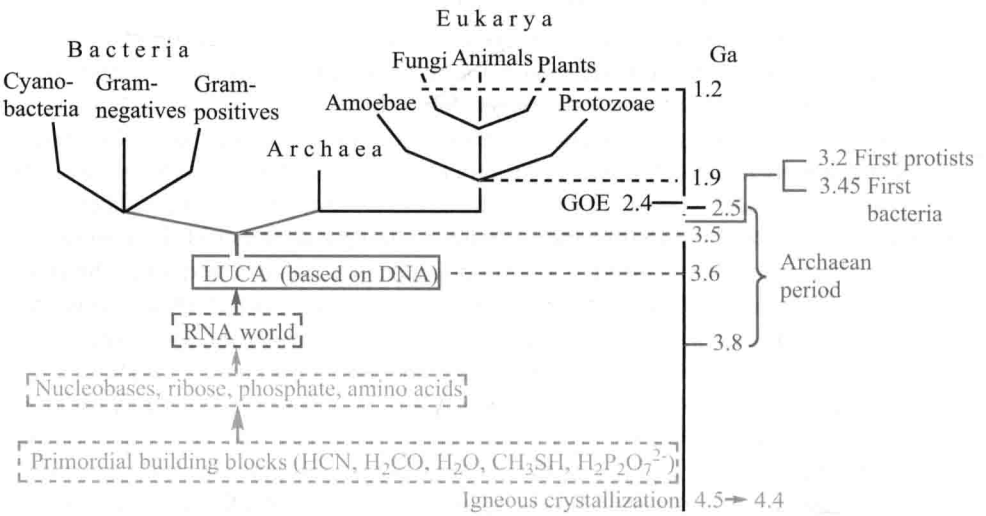
2.1 What is Life, and how did Life evolve?

The study of bioinorganic chemistry can help us probe questions such as (i) 'How did life evolve on Earth?'; (ii) 'Are life forms resembling ours also feasible on other planets/moons in our Solar System, or on exoplanets?'; and (iii) 'Can alternative (e.g. non-carbon and non-water) life forms exist?'. The first question in particular can be explored via pre-life scenarios, such as those provided by the Miller-Urey and related experiments, 'clay-organisms', as originally proposed by Cairns-Smith, or 'pioneer organisms' in a primordial iron-sulfur world (Wächtershäuser), as explained in Sidebar 2.1. The comparatively high concentrations of K^+,

Zn^{2+}, Mn^{2+}, and phosphate in modern cells, exceeding the respective concentrations in common aqueous habitats (such as oceans, lakes, and rivers), suggests that primordial volcanic ponds of condensed geothermal vapour, nestling between silicateous and sulfidic rock, acted as hatcheries for the protocells.[1]

In addition to considering primordial scenarios for the development of the first cells and their adaption to an alleged inhospitable environment, the study of 'modern' extremophiles on our planet can help to answer questions such as those set out above. Commonly, extremophiles (for more details see below) are bacteria and archaea, subsumed under the term prokarya (or prokaryota) as opposed to eukarya, which thrive under conditions where 'normal' microorganisms cannot exist. In rare cases, horizontal gene transfer from prokarya to algae can also provide eukarya with the ability to live in extreme conditions.

Scheme 2.1 provides an approximate time line for the development of terrestrial life. Our planet accreted from the presolar nebula 4.56 Ga ago (1 Ga = 10^9 years). Igneous crystallization, providing an initial, still fragile crust, started about 4.53 Ga ago; the oldest minerals found on Earth, micron-sized zircon ($ZrSiO_4$) crystals, date back to 4.4 Ga. The primordial atmosphere consisted of molecular species such as CO_2, N_2, NH_3, H_2, and H_2O (and likely trace amounts of O_2). Simple inorganic, organic, and transient molecules and ions derived from this primordial atmosphere, such as H_2O, HCN, CO/CO_2, H_2CO, and CH_3SH, provide,



Scheme 2.1 A time line (in billion years, Ga; not to scale) for the development of pre-life and life forms on Earth, including a simplified phylogenetic tree. Colour code: Building blocks for life molecules in light blue, Archaean period in blue, the three trees of life (bacteria, archaea, eukarya)[2] in black. LUCA = last uniform common ancestor. RNA and DNA = ribo- and deoxyribonucleic acid. GOE = Great Oxygen Event. Contrasting prokarya (bacteria and archaea), eukaryotic cells possess a nucleus and differentiated cell organelles (such as mitochondria and chloroplasts). Bacteria and archaea are distinguished by the lipids employed in the cell walls (ester lipids in the case of bacteria; terpenoid ether lipids in the case of archaea).

1 For details, see Suggested reading (Mulkidjanian et al.).

2 An organism dubbed 'Myoyin parakaryote', with intermediate features between prokarya and eukarya, has recently been reported [4].

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