

1 Historical Background, Current Relevance and Perspectives

The progress of an inorganic chemistry of biological systems has had a curious history.

R. J. P. WILLIAMS, *Coord. Chem. Rev.* **1990**, 100, 573

The description of a rapidly developing field of chemistry as “bioinorganic” seems to involve a contradiction in terms, which, however, simply reflects a misconception going back to the beginning of modern science. In the early 19th century, chemistry was still divided into an “organic” chemistry which included only substances isolated from “organisms”, and an “inorganic” chemistry of “dead matter”.¹ This distinction became meaningless after Wöhler’s synthesis of “organic” urea from “inorganic” ammonium cyanide in 1828. Nowadays, organic chemistry is defined as the chemistry of hydrocarbons and their derivatives, with the possible inclusion of certain nonmetallic heteroelements such as N, O and S, regardless of the origin of the material.

The increasing need for a collective, not necessarily substance-oriented designation of the chemistry of living organisms then led to the new term “biochemistry”. For a long time, classical biochemistry was concerned mainly with organic compounds; however, the two areas are by no means identical.² Improved trace analytical methods have demonstrated the importance of quite a number of “inorganic” elements in biochemical processes and have thus revealed a multitude of partially inorganic natural products. A corresponding list would include:

- metalloenzymes (ca. 40% of the known enzymes, especially oxidoreductases (**Fe**, **Cu**, **Mn**, **Mo**, **Ni**, **V**) and hydrolases (e.g. peptidases, phosphatases: **Zn**, **Mg**; **Ca**, **Fe**);
- nonenzymatic metalloproteins (e.g. hemoglobin: **Fe**);
- low-molecular-weight natural products (e.g. chlorophyll: **Mg**);
- coenzymes, vitamins (e.g. vitamin B₁₂: **Co**);
- nucleic acids: (e.g. DNAⁿ⁻(M⁺)_n, M = **Na**, **K**);
- hormones (e.g. thyroxine, triiodothyronine: **I**);
- antibiotics (e.g. ionophores: valinomycin/**K**);
- biominerals (e.g. bones, teeth, shells, coral, pearls: **Ca**, **Si**, ...).

¹There is increasing evidence that much of the “inorganic” material on the surface of the earth has undergone transformations during long-term contact with organisms and their metabolic products, such as O₂ [1].

²The term “bioorganic chemistry” is increasingly being used for studies of organic compounds that are directly relevant for biochemistry.

Some (by today's definition) "inorganic" elements were established quite early as essential components of living systems. Examples include the extractions of potassium carbonate (K_2CO_3 , potash) from plants and of iron-containing complex salts $\text{K}_{3,4}[\text{Fe}(\text{CN})_6]$ from animal blood in the 18th century, and the discoveries of elemental phosphorus (as P_4) by dry distillation of urine residues in 1669 and of elemental iodine from the ashes of marine algae in 1811.

In the middle of the 19th century, Liebig's studies on the metabolism of inorganic nutrients, especially of nitrogen, phosphorus and potassium salts, significantly improved agriculture, so that this particular field of science gained enormous practical importance. However, the theoretical background and the analytical methods of that time were not sufficient to obtain detailed information on the mechanism of action of essential elements, several of which occur only in trace amounts. Some very conspicuous compounds which include inorganic elements like iron-containing hemoglobin and magnesium-containing chlorophyll, the "pigments of life", were analyzed and characterized later within a special subfield of organic chemistry, the chemistry of natural products. It was only after 1960 that bioinorganic chemistry became an independent and highly interdisciplinary research area.

The following factors have been crucial for this development:

1. Biochemical isolation and purification procedures, such as chromatography, and the new physical methods of trace element analysis, such as atomic absorption or emission spectroscopy, require ever smaller amounts of material. These methodical advances have made it possible not only to detect but also to chemically and functionally characterize trace elements or otherwise inconspicuous metal ions in biological materials. An adult human being, for example, contains about 2 g of zinc in ionic form (Zn^{2+}). Although zinc cannot be regarded as a true trace element, the unambiguous proof of its existence in enzymes was established only in the 1930s. Genuine bioessential trace elements such as nickel (Figures 1.1 and 1.2), (Chapter 9) and selenium (Chapter 16.8) have been known to be present as constitutive components in several important enzymes only since about 1970.

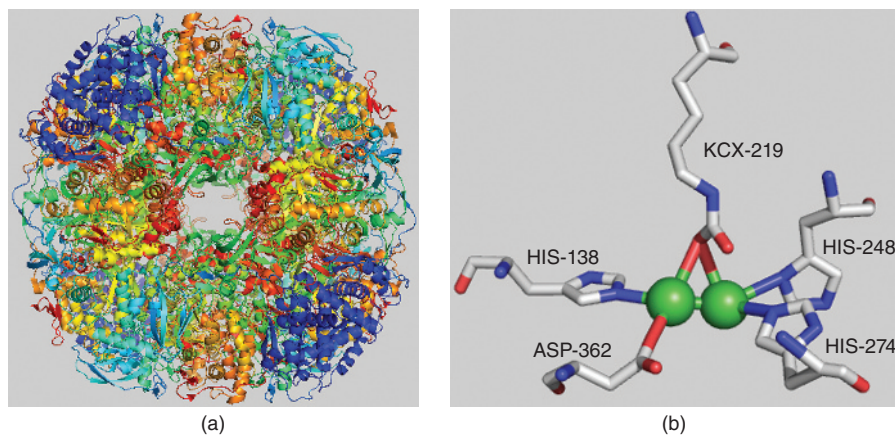
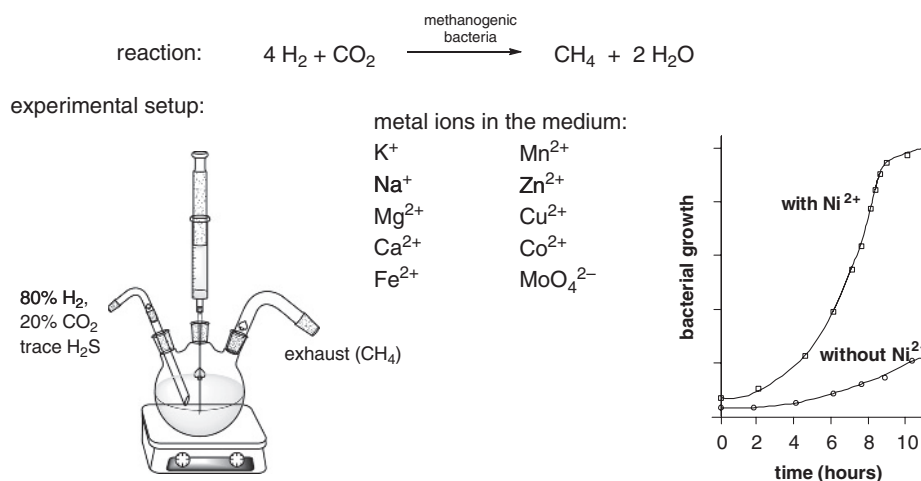


Figure 1.1

Nickel-containing urease, the first enzyme to be crystallized [2]. (a) Crystal structure of the full assembly of *Helicobacter pylori* urease, redrawn from [3] (PDB code 1E9Z). (b) Active site with two nickel centers (green spheres); histidine, aspartate, and a carbamylated lysine as ligands (Section 9.2).

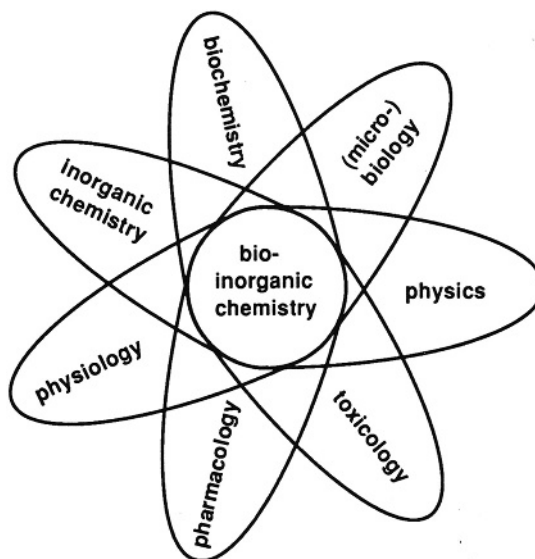
**Figure 1.2**

Discovery of nickel as an essential trace element in the production of methane by archaea.

In a desire “to accomplish something of real importance”, the biochemist James B. Sumner managed to isolate and crystallize in 1926 a pure enzyme for the first time [2], much to the skepticism and disbelief of most experienced scientists. The chosen enzyme, urease (from jack beans), catalyzes the hydrolysis of urea, $\text{O}=\text{C}(\text{NH}_2)_2$, to CO_2 and 2NH_3 . It contains two closely associated nickel ions per subunit (Section 9.2). It was believed by many then that pure enzymes contained no protein, and only after other enzymes were crystallized was Sumner’s discovery accepted. He was honored in 1946 with the Nobel Prize in Chemistry. However, Sumner’s belief that urea contained *only* protein was corrected in 1975 when Dixon *et al.* proved that urease is a nickel metalloenzyme (Section 9.2).

In a very different research area, the biological reduction of carbon dioxide by hydrogen to produce methane has been investigated by studying the relevant archaeobacteria, which are found, for example, in sewage plants. Even though the experiments were carried out under strictly anaerobic conditions and all “conventional” trace elements were supplied (Figure 1.2), the results were only partly reproducible. Eventually it was discovered that during sampling with a syringe containing a supposedly inert stainless steel (Fe/Ni) tip, minute quantities of nickel had dissolved. This inadvertent generation of Ni^{2+} ions led to a distinctive increase in methane production [4], and, in fact, several nickel containing proteins and coenzymes have since been isolated (see Chapter 9). Incidentally, a similar unexpected dissolution effect of an apparently “inert” metal led to the serendipitous discovery of the inorganic anti-tumor agent $\text{cis-PtCl}_2(\text{NH}_3)_2$ (“cisplatin”, Section 19.2.1).

2. Efforts to elucidate the mechanisms of organic, inorganic and biochemical reactions have led to an early understanding of the specific biological functions of some inorganic elements. Nowadays, many attempts are being made to mimic biochemical reactivity

**Figure 1.3**

Bioinorganic chemistry as a highly interdisciplinary research field.

through studies of the reactivity of model systems, low-molecular-weight complexes or tailored metalloproteins (Section 2.4).

3. The rapid progress in bioinorganic chemistry, an interdisciplinary field of research (Figure 1.3), has been made possible through contributions from:
 - physics (→ techniques for detection and characterization);
 - various areas of biology (→ supply of material and specific modifications based on site-directed mutagenesis);
 - agricultural and nutritional sciences (→ effects of inorganic elements and their mutual interdependence);
 - pharmacology (→ interaction between drugs and endogeneous or exogeneous inorganic substances);
 - medicine (→ imaging and other diagnostic aids, chemotherapy);
 - toxicology and the environmental sciences (→ potential toxicity of inorganic compounds, depending on the concentration).

A list of examples illustrating the *application potential of bioinorganic chemistry* could include the following:

- Industrial sector:
 - anaerobic bacterial degradation in sewage plants or in sediments: **Fe, Ni, Co**;
 - biomining (bacterial leaching; ≈ 15% of the global copper production): **Cu, Au, Fe, U**.
- Environmental sector:
 - agricultural trace element problems: nitrogen fixation (**Fe, Mo, V**); **Mo/Cu** antagonism; **Se** content of soil;
 - pollution through metal species: **Pb, Cd, Hg, As, Al, Cr**;
 - detoxification, for example via peroxidases: **Fe, Mn, V**.

[illegible]

Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
18.2			18.2										
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr
18.2		18.2		18.2									

Figure 1.4

Periodic table of the elements. Indicated are the chapters and sections in which each element is discussed in this book.

presumably essential element for human beings.

- Biomedical sector:
 - radiodiagnostics (single-photon emission computed tomography (SPECT), positron emission tomography (PET)), radiotherapy: **Tc, I, Ga, In, Re**;
 - other imaging techniques (magnetic resonance imaging (MRI), x-ray: **Gd, Ba, I**);
 - chemotherapy: **Pt, Au, Li, B, Bi, As**;
 - biominerals (biocompatible materials, coping with demineralization processes): **Ca, P, C, F**;
 - “inorganic” nutrients and noxious food components: deficiency, poisoning; physiological dynamics of resorption, transport, storage, excretion;
 - drug development (oxidative metabolism, metalloenzyme inhibitors): **Fe, Zn**;
 - biotechnological options: specific mutation, metalloprotein design.

A particularly spectacular example of applied bioinorganic chemistry is the successful use of the simple inorganic complex *cis*-diamminedichloroplatinum, *cis*-Pt(NH₃)₂Cl₂ (“cisplatin”), in the therapy of certain tumors (Section 19.2). This compound has been the subject of one of the most successful patent applications ever granted to a university.

Even those areas of chemistry that are not primarily biologically oriented can profit from the research in bioinorganic chemistry. Due to the relentless pressure of evolutionary selection, biological processes show a high efficiency under preset conditions. These continuously self-optimizing systems can therefore serve as useful models for problems in modern chemistry. Among the most current topics of this type are:

- the efficient collection, conversion and storage of energy;
- the catalytic activation of inert substances, especially of small molecules under mild conditions in stepwise fashion;
- the (stereo)selective synthesis of high-value substances with minimization of the yield of unwanted byproducts; and
- the environmentally benign degradation and recycling of substances, especially the detoxification or recycling of chemical elements from the periodic table (Figure 1.4).

Beyond a presentation and description of bioinorganic systems, the major purpose of this book is to reveal the correlation of function, structure and actual reactivity of inorganic elements in organisms. The more biological than chemical question of “Why?” should eventually stimulate a more purposeful use of chemical compounds in nonbiological areas as well.

References

1. R. M. Hazen, *The Story of Earth*, Viking, New York, **2012**.
2. R. D. Simoni, R. L. Hill, M. Vaughan, *J. Biol. Chem.* **2002**, 277, e23: *Urease, the first crystalline enzyme and the proof that enzymes are proteins: the work of James B. Sumner*.
3. B. E. Dunn, M. G. Grutter, *Nat. Struct. Biol.* **2001**, 8, 480–482: *Helicobacter pylori springs another surprise*.
4. P. Schönheit, J. Moll, R. K. Thauer, *Arch. Microbiol.* **1979**, 123, 105–107: *Nickel, cobalt, and molybdenum requirement for growth of methanobacterium thermoautotrophicum*.