

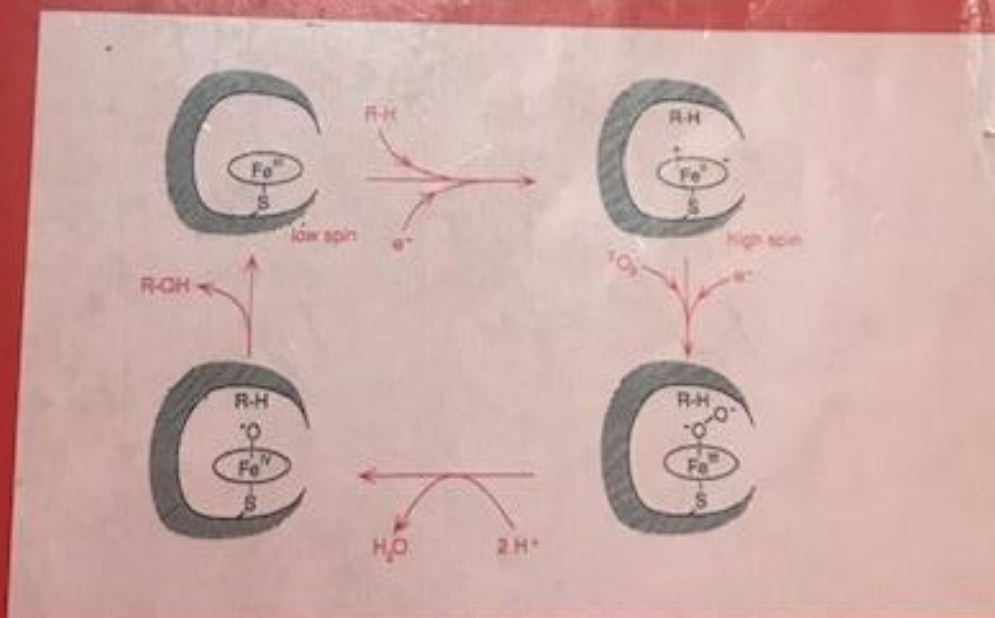
Unit -1 --Bioinorganic and bio Physical

Metal ion in biological system, Material related to your Paper and Lectures.


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Brigitte Schwederski

# Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life

*An Introduction and Guide*



INORGANIC CHEMISTRY  
A Textbook Series

 WILEY  
Publishers Since 1807

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Li 19.5	Be 17.7															B (6.2, 18.3) (12.2)	C (11.2) (11.3)	N (14.1) (15)	O (5)	F 15, 16.6	Ne
Na 4.2, 13	Mg 14.1, 15															Al 17.5	Si 15, 18.2	P (14.1) (15)	S (7.1)	Cl (13.4)	Ar
K 3.9, 13, 14.1, 16	Ca 4.3, 13	Sc	Y	Sc	Ti 99.3	V 91.3, 11.4	Cr 4.3, 6.3	Mn 10.5, 12	Fe 10.5, 12	Co 1.9	Ni 10.18	Cu 10.18	Zn 10.4	Ga 2.3, 2	Ge 76.4, 12.7	As 19.9	Se 16.5	Br 18.2	Kr		
Rb 16.2	Sr 15, 18.2	Zr 98.3	Nb 11.1	Mo 11.2	Tc 18.3	Ru 15.2	Rh 18.3	Pd 17.3	Ag 17.3	Cd 18.3	In 18.3	Sn 18.3	Sb 18.2	Te 18.2	I 16.7	Xe 18.2	At 18.3	Po 18.2	Rn		
Cs 16.2	Ba 15, 18.2	Hf 18.3	Ta 11.1	W 18.3	Re 18.3	Os 19.2	Ir 19.4	Pt 18.3	Au 17.5	Hg 17.4	Tl 18.3	Pb 18.3	Bi 19.1	Po 18.2	At 18.2	Rn					
Fr 18.2	Ra 14.2	Ac																			

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

Figure 1.3

Periodic table of the elements. Indicated are the chapters (italicized) in which the corresponding element is discussed in this book:  essential element  presumably essential element for human beings

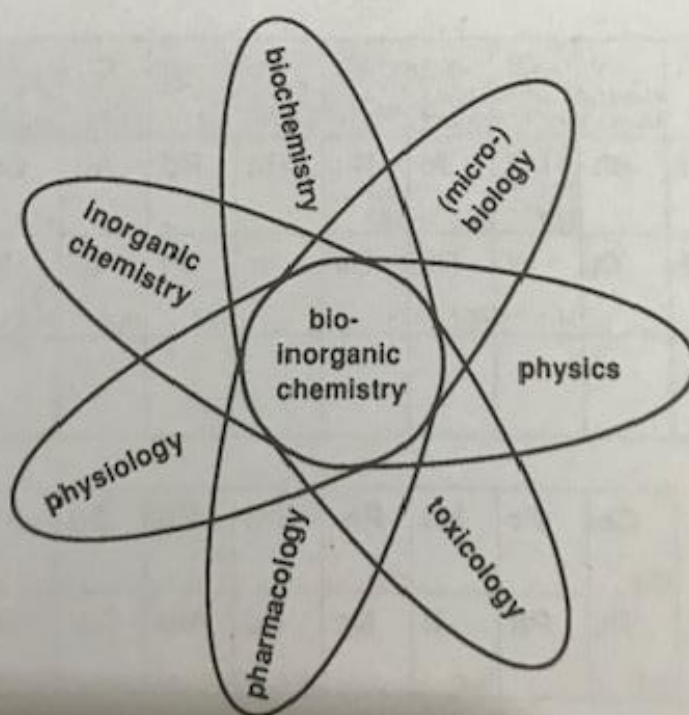
**Table 2.1** Average elemental composition of a human body (adult, 70 kg [1])

element and symbol		mass (g)	year of discovery as an essential element
oxygen	O	45500	
carbon	C	12600	
hydrogen	H	7000	
nitrogen	N	2100	
calcium	Ca	1050	
phosphorus	P	700	
sulfur	S	175	
potassium	K	140	
chlorine	Cl	105	
sodium	Na	105	
magnesium	Mg	35	
iron	Fe	4.2	17th century
zinc	Zn	2.3	1896
silicon	Si	1.4	1972
rubidium*	Rb	1.1	
fluorine	F	0.8	1931
zirconium*	Zr	0.3	
bromine*	Br	0.2	
strontium*	Sr	0.14	
copper	Cu	0.11	1925
aluminum*	Al	0.10	
lead*	Pb	0.08	
antimony*	Sb	0.07	
cadmium*	Cd	0.03	(1977)
tin*	Sn	0.03	(1970)
iodine	I	0.03	1820
manganese	Mn	0.02	1931
vanadium*	V	0.02	(1971)
selenium	Se	0.02	1957
barium*	Ba	0.02	
arsenic*	As	0.01	1975
boron*	B	0.01	
nickel*	Ni	0.01	(1971)
chromium	Cr	0.005	1959
cobalt	Co	0.003	1935
molybdenum	Mo	< 0.005	1953
lithium*	Li	0.002	

not essential. \* Essentiality uncertain.

elements, fall within the range of iron and zinc with amounts totalling about 1 g each. The relative amounts of the genuine trace elements is smaller by at least another order of magnitude, and some of them have not yet been unambiguously defined with regard to amount, essential character and function [2]. Strictly speaking, elements should be called *essential* only if their total absence in the organism causes severe, irreversible damage. Frequently, essentiality is now already being invoked if the optimal functioning of organisms is impaired; in such instances the corresponding elements may better be referred to as 'beneficial'. Table 2.1 also illustrates the

- (i) physics (→ techniques for detection and characterization),
- (ii) various areas of biology (→ supply of material and, more recently, specific modifications based on site-directed mutagenesis),
- (iii) agricultural and nutritional sciences (→ effects of inorganic elements and their mutual interdependence),
- (iv) pharmacology (→ interaction between drugs and endogeneous or exogeneous inorganic substances),
- (v) medicine (→ diagnostic aids, tumor therapy),
- (vi) toxicology and the environmental sciences (→ potential toxicity of inorganic compounds, the 'concentration problem' [3]).



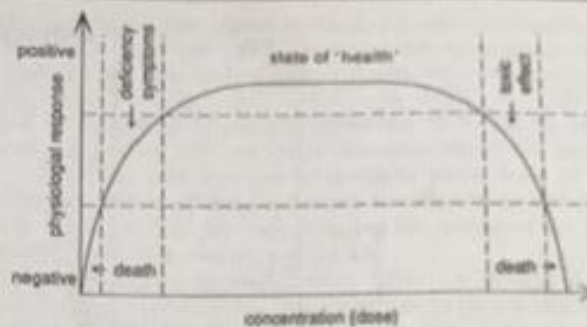


Figure 2.3  
Schematic dose-response diagram for an essential element (compare Figure 17.1 for exclusively toxic elements)

the ambivalent effects of many substances and illustrates the principle of Paracelsus: 'The dose makes the poison.' An important term here is that of the *therapeutic width* which characterizes the concentration range causing advantageous physiological effects.

In a more detailed approach, the following aspects have to be considered:

- The chemical compound of which the element is a part is often crucial for the response of the organism (chemical speciation). The pathway, the extent and rate of uptake, metabolism, storage and excretion can differ greatly; poor utilization of an otherwise bioavailable essential trace element may thus be responsible for deficiency symptoms. The absorption of inorganic compounds by the organism depends primarily on the solubility and, therefore, on the charge of the system; humans resorb molybdate  $\text{MoO}_4^{2-}$  to about 70–80% from food whereas slowly reacting  $\text{Cr}^{3+}$  is resorbed only to a small extent (<1%).
- It cannot be expected that higher organisms react uniformly within a population or in the course of their individual development. Therefore, only average statements can be made with regard to a certain situation, e.g. for the adult state of a preferentially homogeneous population (Figure 2.4).
- The concentration variation of one particular element generally affects the concentrations and physiological effects of other substances, including other inorganic elements. This multidimensional interdependence has been known qualitatively for a number of elemental nutrients since the experiments of Liebig. Two components can interact by mutually promoting corresponding effects (synergism) or by competing and suppressing each other's effects (antagonism, Figure 2.5).

An antagonistic relationship in a two-component system can be the result of displacement ( $\text{Zn}^{2+} \leftrightarrow \text{Cd}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Cu}^{2+}$  or  $\text{Ca}^{2+}$ ) or mutual deactivation:  $\text{Cu}^{2+} + \text{S}^{2-} \rightarrow \text{CuS}$  (insoluble). With three components, e.g. in the system Cu/Mo/S (Chapter 10 and Section 11.1.2), matters become more complicated and, in reality, there is a multidimensional network of synergistic and antagonistic relationships which is further complicated by the spatially unsymmetrical distribution of inorganic

Table 2.2 Some characteristic symptoms of chemical element deficiency in humans

deficient element	typical deficiency symptoms
Ca	retarded skeletal growth
Mg	muscle cramps
Fe	anemia, disorders of the immune system
Zn	skin damage, stunted growth, retarded sexual maturation
Cu	artery weakness, liver disorders, secondary anemia
Mn	infertility, impaired skeletal growth
Mo	retardation of cellular growth, propensity for caries
Co	pernicious anemia
Ni	growth depression, dermatitis
Cr	diabetes symptoms
Si	disorders of skeletal growth
F	dental caries
I	thyroid disorders, retarded metabolism
Se	muscular weakness, esp. cardiomyopathy
As	impaired growth (in animals)

incomplete list in Table 2.2). As far as causal connections are known for the single elements, these will be discussed in the corresponding chapters within this book. A general syndrome of (trace) element deficiency is growth retardation; the number of truly essential elements seems to be smaller in fully developed organisms than during growth periods. This assumption was confirmed by the pioneering experiments in the 1960s which were designed to guarantee a nutritionally complete diet for astronauts during longer space flights. The inorganic contents of such synthetic food are summarized in Table 2.3 in the form of the RDA (recommended dietary allowances) values of the American Food and Drug Administration [9]. Whether such a composition is really sufficient, how much of it occurs in today's food supply and how far it can be exceeded via increased uptake or separate supplementation without detrimental consequences are still open questions in dietetics, particularly from the popular scientific point of view.

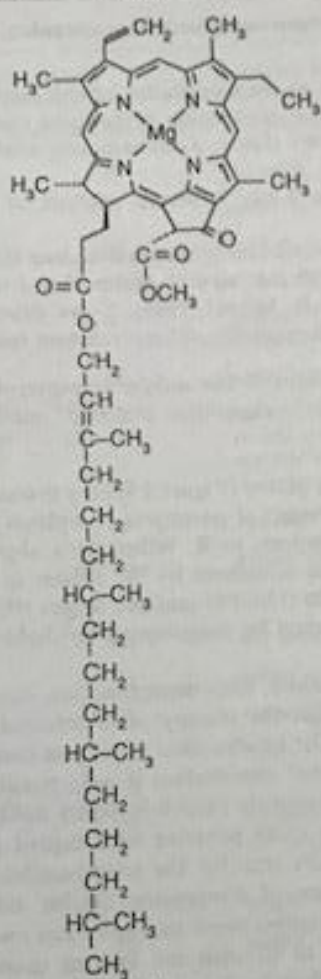
## 2.2 Biological Functions of Inorganic Elements

The great efforts made by organisms to take up, accumulate, transport and store inorganic elements is justified only by their important and otherwise not guaranteed function. For living organisms, the arbitrary distinction between 'organic' and 'inorganic' compounds is irrelevant since it is solely based on a historically grown definition. However, there are functions like those listed below for which compounds or ions of the metals are particularly well suited:

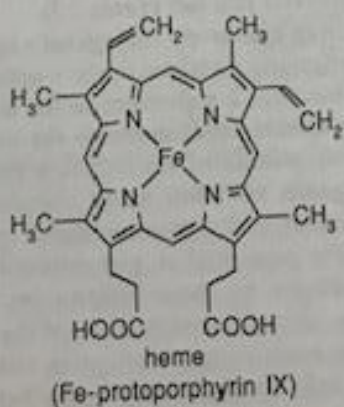
- (a) The assembly of hard structures in the form of endo- or exoskeletons via biomineralization certainly falls into this category (Chapter 15). Another aspect of this *structural function* is that cell membranes require the presence of metal ions to cross-link the organic 'filling material' and thus maintain the membrane integrity. Even the double helical structure of DNA (a polyanion) is maintained only in the presence of mono- and divalent cations which significantly reduce the otherwise dominating electrostatic repulsion forces between the negatively charged nucleotide phosphate groups [14]. Solid-state/structural functions are represented mainly by the elements Ca, Mg (as dications) and P, O, C, S, Si, F (as parts of anions).



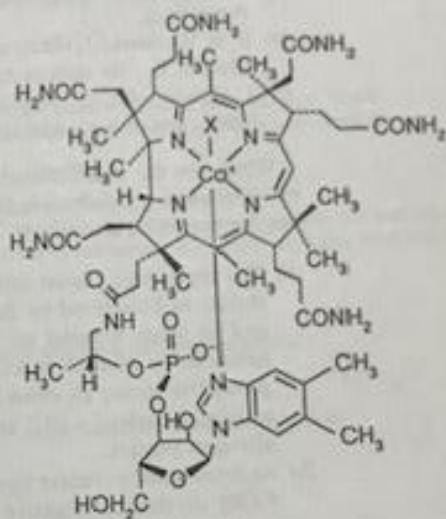
- (b) Simple atomic ions are superbly suited as *charge carriers* for very fast *information transfer*. Starting with a transmembrane concentration gradient which has to be actively maintained by integral membrane ion pumps, information units in the form of electrical potential jumps can be created via diffusion, i.e. with maximal speed (biological selection) along ion channels. Electrical impulses in nerves as well as more complex trigger mechanisms, e.g. in the control of muscle contractions, are thus initiated with the fastest possible effect by sudden fluxes (diffusion control) of atomic, i.e. chemically and biologically nondegradable inorganic ions of different size and charge ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ; see Chapter 13 and Section 14.2).
- (c) *Formation, metabolism and degradation of organic compounds* in organisms often require acid or base catalysis. Since the physiological pH is generally limited to about 7, except for certain special compartments such as the stomach, the rate enhancement of such reactions cannot be accomplished by simple proton or hydroxide catalysis but requires *Lewis acid/Lewis base catalysis* involving metal ions. Many hydrolytically active enzymes thus contain the relatively small, positively charged metal ions  $\text{Zn}^{2+}$  and  $\text{Mg}^{2+}$  (Chapter 12 and Section 14.1).
- (d) The *transfer of electrons* which is essential for the short-term *energy conversion* in organisms is mainly, but not exclusively, dependent on redox-active metal centers. A number of corresponding redox pairs has thus been found, some of which involving oxidation states that seem quite unusual under physiological conditions (marked in bold in the following). Specific modifications induced by 'bioligands' are largely responsible for the stabilization of such 'unusual' oxidation states. Biologically relevant are in particular the following oxidation states of redox-active metals:  $\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}/\text{Fe}^{\text{IV}}$ ,  $\text{Cu}^{\text{I}}/\text{Cu}^{\text{II}}$ ,  $\text{Mn}^{\text{II}}/\text{Mn}^{\text{III}}/\text{Mn}^{\text{IV}}$ ,  $\text{Mo}^{\text{IV}}/\text{Mo}^{\text{V}}/\text{Mo}^{\text{VI}}$ ,  $\text{Co}^{\text{I}}/\text{Co}^{\text{II}}/\text{Co}^{\text{III}}$ ,  $\text{Ni}^{\text{I}}/\text{Ni}^{\text{II}}/\text{Ni}^{\text{III}}$ .
- (e) The *activation of small, highly symmetrical molecules* with large bond energies places stringent demands on the required catalysts. The ability of transition metal centers to provide unpaired electrons and to simultaneously accept and donate electronic charge ( $\pi$  back-bonding; see Chapters 5 and 11) allows organisms to carry out energetically and mechanistically difficult reactions under physiological conditions, e.g.
- (i) the reversible uptake, transport, storage and conversion (Fe, Cu) and also the generation (Mn) of the paramagnetic dioxygen molecule,  $^3\text{O}_2$  (Chapters 4 to 6 and 10),
  - (ii) the fixation of molecular nitrogen,  $\text{N}_2$  (Chapter 11), and its conversion to ammonia (Fe, Mo, V), or
  - (iii) the reduction of  $\text{CO}_2$  with hydrogen to give methane (Ni, Fe; Chapter 9 and Figure 1.1).
- (f) Typical '*organometallic*' reactivity such as reductive alkylation or the *facile generation of radicals* for rapid rearrangement of substrate molecules is found for cobalamin coenzymes which contain a  $\sigma$  bond between the transition metal cobalt and primary alkyl groups (Chapter 3).



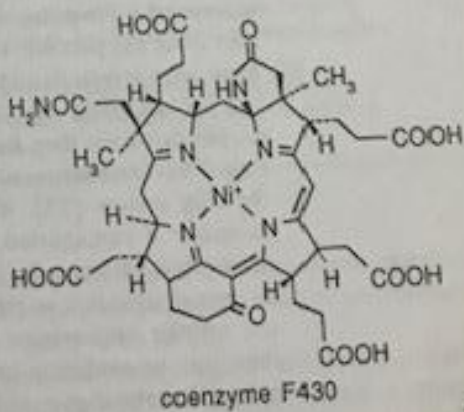
chlorophyll a



heme  
(Fe-protoporphyrin IX)



vitamin B<sub>12</sub> (X = CN)



coenzyme F430

(2.5)

**Table 2.3** Essential elements in food for adults and infants

inorganic constituents	recommended daily allowances (in mg)	
	adult*	infant*
K	2000 - 5500	530
Na	1100 - 3300	260
Ca	800 - 1200	420
Mg	300 - 400	60
Zn	15	5
Fe	10 - 20	7.0
Mn	2.0 - 5	1.3
Cu	1.5 - 3	1.0
Mo	0.075 - 0.250	0.06
Cr	0.05 - 0.2	0.04
Co	ca. 0.2 (vitamin B <sub>12</sub> )	0.001
Cl	3200	470
PO <sub>4</sub> <sup>3-</sup>	800 - 1200	210
SO <sub>4</sub> <sup>2-</sup>	10	
I	0.15	0.07
Se	0.05 - 0.07	
F	1.5 - 4.0	0.6

\* Mainly from Recommended Dietary Allowances, RDA; National Academy of Sciences, USA.

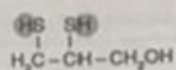
\* Estimated from producers' tables of contents of typical SL(Sine Lacte) food for infants.

**Table 2.4** Chelate ligands for detoxification after metal poisoning

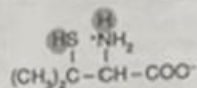
ligand (formulae 2.1)	trade or trivial name	preferably coordi- nated metal ions	detailed description in Chapter
(a) 2,3-dimercapto-1-propanol	dimercaprol, BAL	Hg <sup>2+</sup> , As <sup>3+</sup> , Sb <sup>3+</sup> , Ni <sup>2+</sup>	17
(b) D-2-amino-3-mercapto-3- methylbutyric acid (D-β,β-dimethylcysteine)*	D-penicillamine	Cu <sup>2+</sup> , Hg <sup>2+</sup>	10, 17
(c) ethylenediaminetetraacetate	EDTA	Ca <sup>2+</sup> , Pb <sup>2+</sup>	
(d) deferoxamine B	DFO, desferal	Fe <sup>3+</sup> , Al <sup>3+</sup>	8.2, 17.6
(e) 3,4,3-LICAMC		Pu <sup>4+</sup>	18.2

\* The L-enantiomer is toxic.

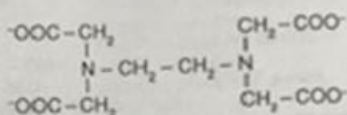
(a)



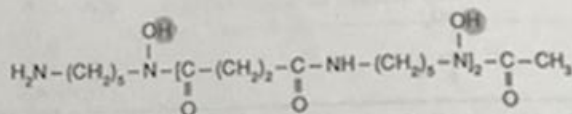
(b)



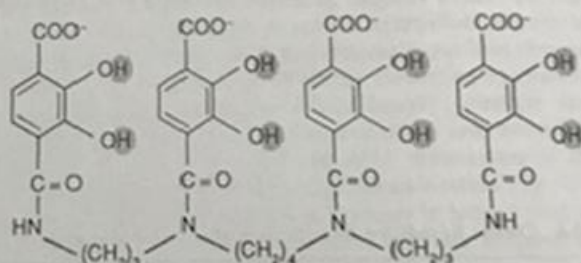
(c)



(d)



(e)



$\text{H}$  : acidic protons  
which may be substituted  
by metal ions

(2.1)

#### 'Hard' and 'Soft' Coordination Centers

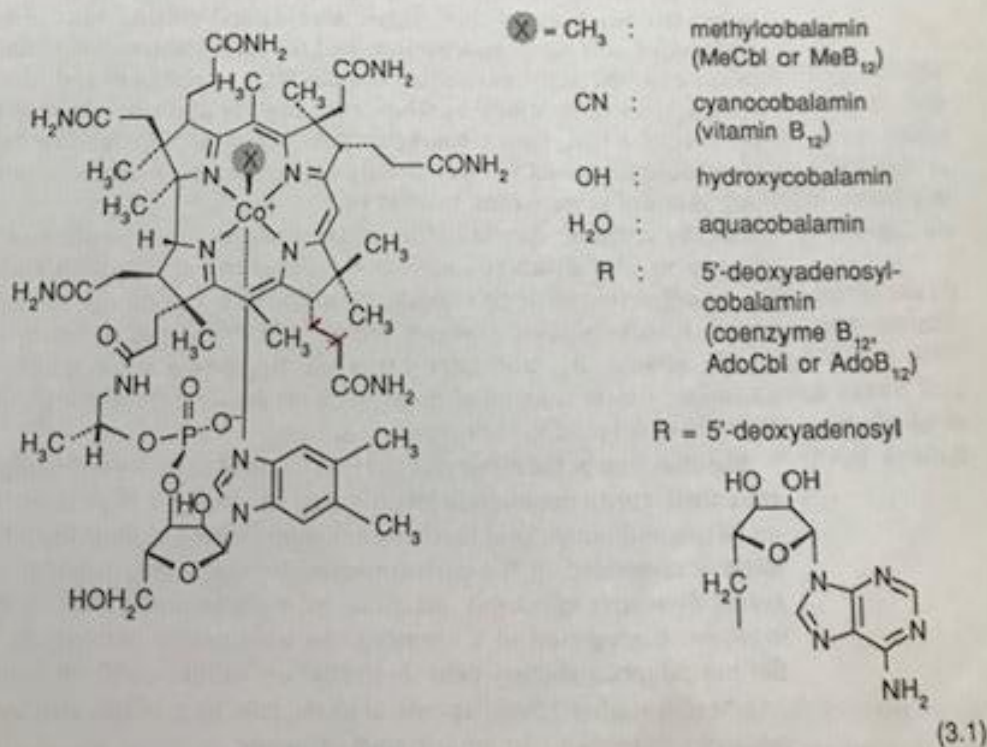
The susceptibility of atoms and ions to experience a charge shift in their electron shell through interaction with a coordination partner differs considerably. This has led to an often loosely used distinction between little affected 'hard' and easily polarizable 'soft' coordination centers. Among the soft electron-pair donors are thiolates ( $\text{RS}^-$ ), sulfides ( $\text{S}^{2-}$ ) and selenides; on the other hand, the

# Cobalamins Including Vitamin and Coenzyme B<sub>12</sub>

## History and Structural Characterization

Coenzyme B<sub>12</sub> and its derivatives (3.1), including vitamin B<sub>12</sub>, are well suited as introductory examples in bioinorganic chemistry for various reasons. First of all, several milestones in the development of the whole field have been associated with vitamin B<sub>12</sub> and later on with the coenzyme. This pertains to the immediate therapeutic benefit, the early use of chromatographic purification methods, the structural elucidation by X-ray crystallography and the relationship between enzymatic and coenzymatic reactivity. Furthermore, modern natural product synthesis as well as bioorganic and organometallic chemistry have strongly profited from studies of the B<sub>12</sub> system.

Coenzyme B<sub>12</sub> (3.1) is a medium-sized molecule with a molecular mass of about 1580 Da which exhibits its characteristic specificity and high reactivity only in combination with corresponding apoenzymes (3.2).



<b>coenzyme</b>	+	<b>apoenzyme</b>	→	<b>holoenzyme</b>
low molecular mass, determines the type of reaction		high molecular mass (protein), determines substrate specificity (selectivity) and the reaction rate		complete enzyme, fully functional
				(3.2)

The incorporation of the element cobalt into the coenzyme is quite surprising because cobalt is the least abundant first-row (3d) transition metal in the earth's crust and in sea water (Figure 2.2). Therefore, a very special functionality is to be expected.

The corrin ligand (2.4) is also unique, particularly with regard to its smaller ring size as compared to the porphyrin systems. Cobalt-containing porphyrin complexes, although stable, are *not* suitable to mimic the actions of coenzyme B<sub>12</sub>.

The sixth, axial metal coordination site in coenzyme B<sub>12</sub> and methylcobalamin features a primary alkyl group (3.1) which makes these complexes the only fully established examples (see Section 9.5) of 'natural' organometallic compounds in biochemistry (see Sections 3.2.4 and 17.3 on the possible bioalkylation of heavy metals). The configuration Co—CH<sub>2</sub>R of alkylcobalamins is unusually stable toward hydrolysis in neutral aqueous solution. On the other hand, the cobalt-carbon bond shows a very special reactivity, viz. the *enzymatically controlled* formation of reactive primary alkyl radicals. This unusual reactivity has prompted chemists from various fields beyond biochemistry to thoroughly study these remarkable complexes [1-3].

In retrospect, during the 1920s it was found that injections of extracts from animal liver were able to cure a very malignant ('pernicious') form of anemia which could otherwise be lethal. Improved methods of trace analysis soon showed that the essential component of these extracts contained cobalt. Since the substance was synthesized only by microorganisms and the trace element cobalt had to be supplied in any case, the factor was called 'vitamin B<sub>12</sub>'. Enrichment and isolation turned out to be extremely laborious; because of the low concentration of only 0.01 mg vitamin per liter of blood, chromatographic separation methods had to be employed. The therapeutically useful but not directly active 'vitaminic' form, cyanocobalamin (3.1), was obtained in pure form in 1948 [4].

As the complete determination of the molecular constitution of cobalamins was impossible with chemical means alone, the eventual structural elucidation required X-ray diffraction of single crystals, a method that could only be applied to relatively simple systems in those days (see Section 4.2). With approximately 100 nonhydrogen atoms, vitamin B<sub>12</sub> and later coenzyme B<sub>12</sub> posed a formidable crystallographic challenge; for the solution of these problems Dorothy Crowfoot-Hodgkin was awarded the 1964 Nobel prize in chemistry.

The structure of the ...