1

INTRODUCTION

The discipline of *bioinorganic chemistry* is concerned with the function of metallic and most of nonmetallic elements in biological processes. Also, it is the study of the chemistry, structure, and reactions of the metalloprotein molecules belonging to the living cell.

The precise concentrations of different ions, for instance, in blood plasma indicate the importance of these ions for biological processes, (Table 1-1).

Such elements fall into four broad classifications: the polluting, contaminating, beneficial, and essential elements.

- Polluting elements: Pb, Hg, and Cd
- Contaminating elements: vary from person to person
- Beneficial elements: Si, V, Cr, Se, Br, Sn, F, and Ni
- Essential elements: H, C, N, O, Na, Mg, K, Ca, P, S, Cl, Mo, Mn, Fe, Co, Cu, Zn, and I (Fig. 1-1).

Twenty-five elements are currently thought to be essential to warm-blooded animals (Table 1-2).

Essentiality has been defined according to certain criteria:

- A physiological deficiency appears when the element is removed from the diet.
- The deficiency is relieved by the addition of that element to the diet.
- A specific biological function is associated with the element.

Chemistry of Metalloproteins: Problems and Solutions in Bioinorganic Chemistry, First Edition.
Joseph J. Stephanos and Anthony W. Addison.

TABLE 1-1 Ion Concentration in Extracellular Blood Plasma

Ion	mM	Ion	mM
Na^+	138	SO_4^{2-}	1
Cl^-	100	Fe	0.02
K^+	4	Zn^{2+}	0.02
Ca^{2+}	3	Cu^{2+}	0.015
Mg^{2+}	1	Co^{2+}	0.002
HPO_4^{2-}	1	Ni^{2+}	0

Every essential element follows a dose–response curve, shown in Fig. 1-2. At lowest dosages the organism does not survive, whereas in deficiency regions the organism exists with less than optimal function.

The ten ions classified as trace metal are Fe, Cu, Mn, Zn, Co, Mo, Cr, Sn, V, and Ni, and the four classified as bulk metals are Na, K, Mg, and Ca. The nonmetallic elements are H, B, C, N, O, F, Si, P, S, Cl, Se, and I.

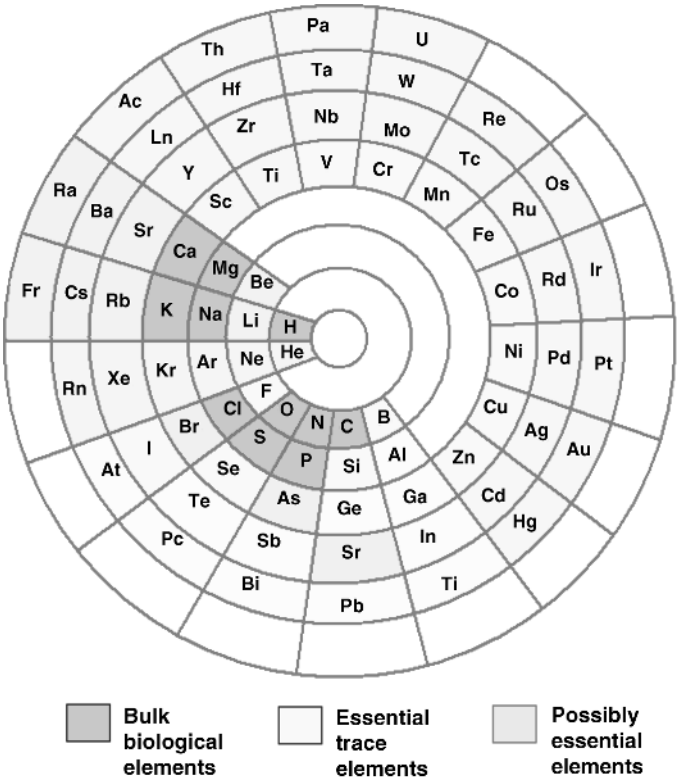


FIGURE 1-1 Distribution of elements essential for life (Cotton and Wilkinson, 1980). (See the color version of this figure in Color Plates section.)

TABLE 1-2 Percentage Composition of Essential Elements in Human Body

Element	Percentage (by Weight)	Element	Percentage (by Weight)
Oxygen	53.6	Silicon	0.04
Carbon	16.0	Iron, fluorine	0.005
Hydrogen	13.4	Zinc	0.003
Nitrogen	2.4	Copper, bromine	2×10^{-4}
Sodium, potassium, sulfur	0.10	Selenium, manganese, arsenic, nickel	2×10^{-5}
Chlorine	0.09	Lead, cobalt	9×10^{-6}

Biological Roles of Metal Ions

What are the general roles of metal ions in biological systems?

The general roles of metal ions in biological systems are summarized in Table 1-3. Metals in biological systems function in a number of different ways:

- Groups 1 and 2 metals operate as *structural* elements or in the *maintenance of charge, osmotic* balance, or *nerve* impulses.
- Transition metal ions that exist in single oxidation states, such as zinc (II), function as structural elements in superoxide dismutase and zinc fingers or as *triggers* for protein activity, e.g., calcium ions in calmodulin or troponin C.

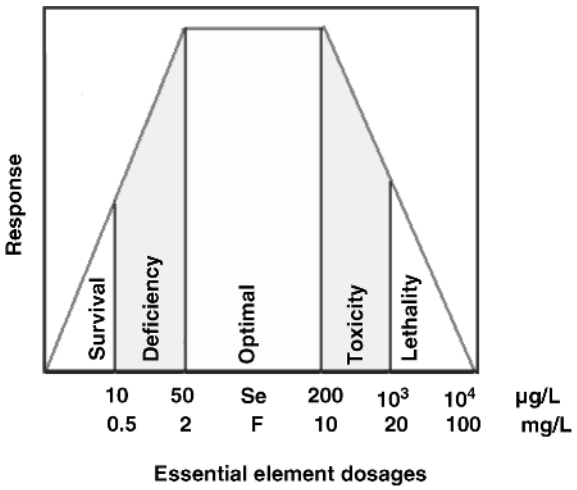


FIGURE 1-2 The dose-response curves of selenium and fluoride.

TABLE 1-3 Role of Metal Ions and Examples

Metal	Functions and Examples
Na^+, K^+	Charge transfer, osmotic balance, nerve impulses
Mg^{2+}	Structure in hydrolases, isomerases, phosphate transfer, and trigger reactions
Ca^{2+}	Structure, charge carrier, phosphate transfer, trigger reactions
Zn^{2+} (tetrahedral)	Structure in zinc finger, gene regulation, anhydnase, dehydrogenase
Zn^{2+} (square pyramidal)	Structure in hydrolases, peptidases
Mn^{2+} (octahedral)	Structure in oxidases, photosynthesis
Mn^{3+} (tetragonal)	Structure in oxidase, photosynthesis
Fe^{2+}	Electron transfer, nitrogen fixation in nitrogenase, dioxygen transport in hemoglobin and myoglobin
Fe^{3+}	Electron transfer in oxidases
Cu^+, Cu^{2+}	Electron transfer in type I blue copper proteins, oxidases and hydroxylases in type II blue copper proteins, hydroxylases in type III blue copper proteins, dioxygen transport in hemocyanin
Co^{2+} (tetrahedral)	Alkyl group transfer, oxidases
Co^+, Co^{2+}, Co^{3+} (octahedral)	Alkyl group transfer in B_{12}
Ni^{2+} (square planar)	Hydrogenase, hydrolases
Mo^{4+}, Mo^{5+}, Mo^{6+}	Nitrogen fixation in nitrogenose, oxo transfer in oxidases

- Transition metals that exist in multiple oxidation states serve as *electron carriers*, e.g., iron ions in cytochromes or in iron–sulfur clusters of the enzyme nitrogenase or copper ions in azurin and plastocyanin.
- As facilitators of *oxygen transport*, e.g., iron ions in hemoglobin or copper ions in hemocyanin.
- As sites at which enzyme *catalysis* occurs, e.g., copper ions in superoxide dismutase or iron and molybdenum ions in nitrogenase.
- Metal ions may serve multiple functions, depending on their location within the biological system, so that the classifications in Table 1-3 are somewhat arbitrary and/or overlapping.

PROTEINS: FORMATION, STRUCTURES, AND METALLOPROTEINS

This section is designed to introduce the chemistry of proteins. The text broadly includes where and how the proteins are formed, along with the structure and formation of metalloproteins.

Following the introduction of organelles and their functions within the cell, the discussion will be concerned with the general structure of deoxyribonucleic acid (DNA) and how the nucleus maintains its control of cell growth, division, and formation of [messenger, transfer, and ribosomal ribonucleic acid (mRNA, tRNA,

rRNA)]. This is followed by how mRNA and tRNA master the formation of proteins within a cell. Then, primary, secondary, tertiary, and quaternary structures of the formed proteins and the factors that control each of these structures are discussed.

Specific points about the ligation of various metal ions to different amino acids within the proteins are made, and the binding stabilities of various metal ions toward different amino acids are arranged.

The general formulas, side chains, and corresponding names of the common natural α-amino acids, the formation of the peptide chain from the amino acids, and the physiological roles of proteins are described.

The chemistry of the prosthetic and cofactors is explored. Enough basic biochemistry is presented to enable the student to understand the discussions that follow.

Organelles and Their Functions

Identify the organelles and their functions within the cell.

- Cells are the building blocks of all living things.
- There are similarities in the appearance, chemical constituents, and activities of all cells (Fig. 1-3).
- Different structures within the cell are called *organelles*.
- Each organelle has an important, specific function in the cell.
- The *mitochondria* are responsible for conversion of food into usable energy (metabolism):
  - They contain enzymes for cell metabolism.
  - More than 50% of the energy produced by mitochondrial oxidation of carbohydrates is recaptured as adenosine diphosphate (ADP) and converted into adenosine triphosphate (ATP).

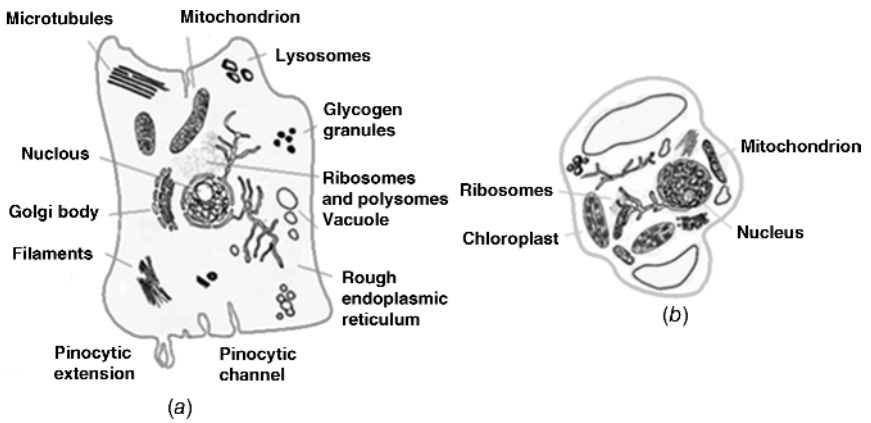
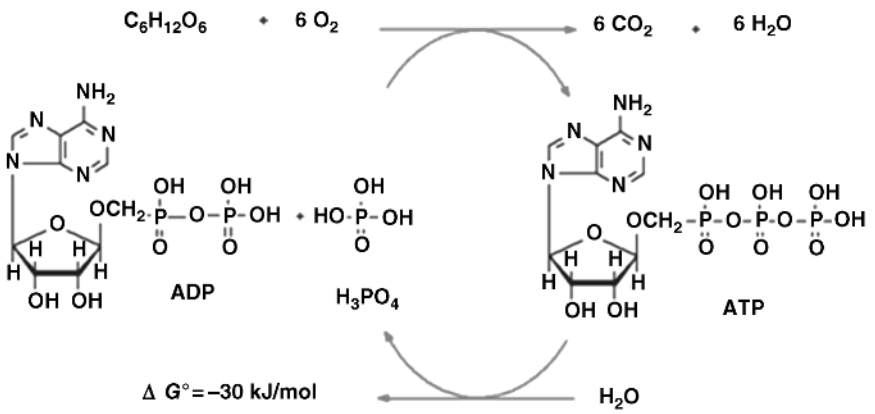


FIGURE 1-3 (*a*) Animal cell and (*b*) plant cell.



SCHEME 1-1 Derived energy is trapped in adenosine triphosphate molecules (ATP).

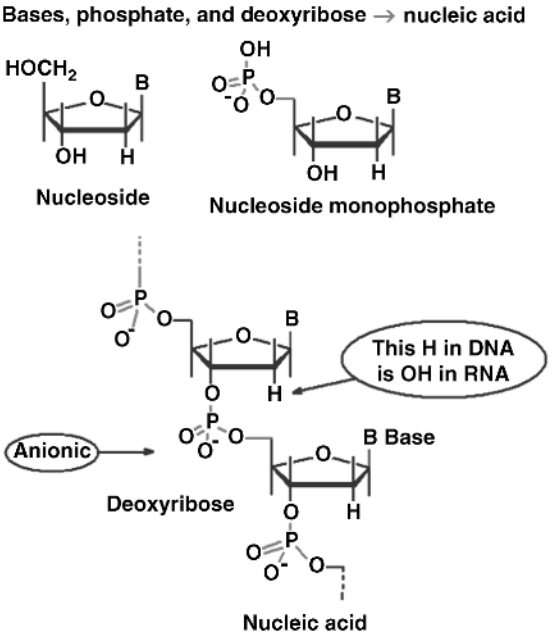
- The derived energy is trapped in ATP molecules (Scheme 1-1).
- ATP can diffuse rapidly throughout the cell, delivering energy to sites where it is required for cellular processes.

- In green plants, *chloroplasts* contain chlorophyll molecules and other pigments.
  - Chlorophyll and other pigments in chloroplasts absorb light energy from the sun and use it to produce ATP, glucose, and oxygen.
- *Ribosomes* are round particles (mRNA) that are sent by the nucleus to activate protein synthesis.
  - The mRNA causes a specific protein molecule to be synthesized from the pool of amino acids present in the cell cytoplasm.
- The *nucleus*, or command station, contains information for the development and operation of the cell.
  - This information is stored chemically in long molecular strands called DNA. A combination of DNA and protein forms fine strands of chromatin. When a cell is about to divide, the chromatin strands coil up and become densely packed, forming chromosomes.
  - The number of chromosomes varies with the species: Humans have 23, the fruit fly has 4, corn has 10, and the mosquito has 3.

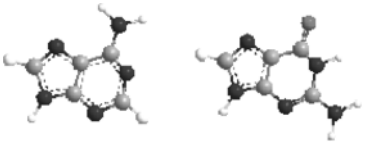
Structure of DNA

What is the general structure of deoxyribonucleic acids, DNA?

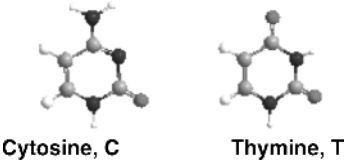
- Polymerization of nucleoside phosphates produces the nucleic acids, DNA and RNA.



- DNA is a giant molecule with molecular weight of order 1 billion or more.
- The information is chemically stored by nitrogen-base molecules that are bonded to the sugar residues of the sugar–phosphate chain.
- There are four nitrogen bases:
  (a) Two purines, which are bicyclic molecules:



  (b) Two pyrimidines, which are monocyclic:



- The order in which they appear on the chain makes up the molecular message (Fig. 1-4).
- The DNA molecule is also capable of duplicating itself and dividing.

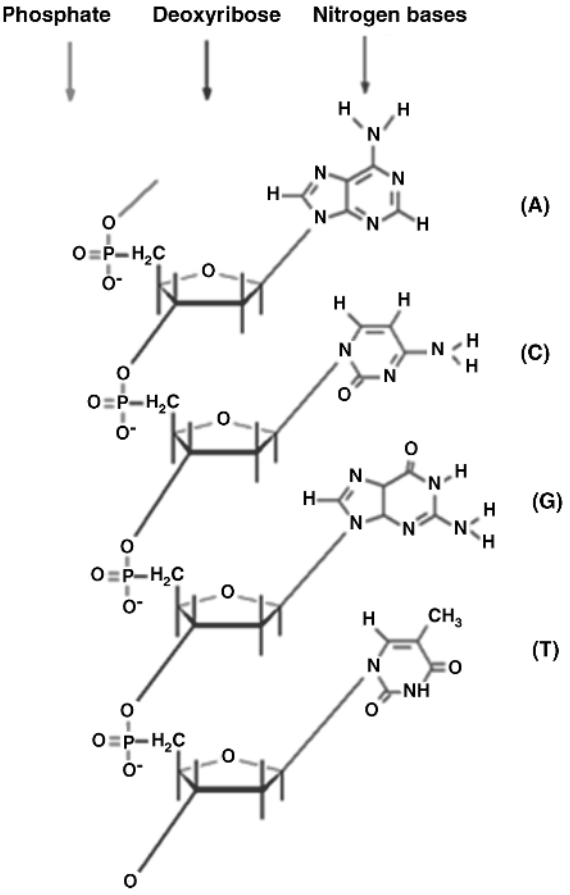
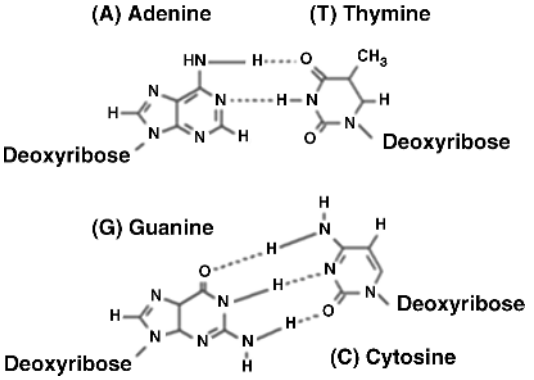


FIGURE 1-4 Order of N bases on chain.

- Under a microscope we can see the duplicated chromosomes divide equally as the cell divides.
- The DNA double strand forms when the bases on the two adjacent single strands form hydrogen bonds:



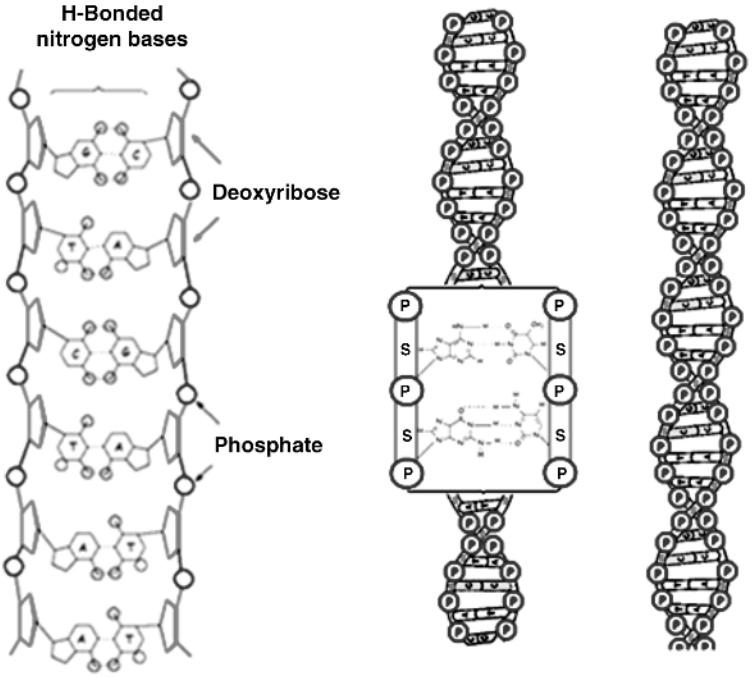


FIGURE 1-5 DNA double strand.

- Adenine and thymine form a hydrogen bonded pair, or *complementary base pair*.
- Cytosine and guanine also form a complementary base pair (Fig. 1-5).
- These complementary base pairs are conformed by the base ratios: G/C = 1 and A/T = 1 (Table 1-4).

TABLE 1-4 Nitrogen-Base Content of DNA from Different Organisms

Species Tissue Source	Calf Thymus	Crab All tissue	Algea (*Euglcna*) Chloroplast	Virus (Coliphaga ×174) Replicative Form
A	29.0	47.3	38.2	26.3
T	28.5	47.3	38.1	26.4
A/T	1.01	1.00	1.00	1.00
G	21.2	2.7	12.3	22.3
C	21.2	2.7	11.3	22.3
G/C	1.00	1.00	1.09	1.00

Note: Data in mole percent.

Cell Growth and Division

How does the nucleus maintain its control of cell growth and division?

- During ordinary cell division called mitosis, two new cells result from a single parent.
- Each daughter has the same number of chromosomes as the parent.
- If DNA is the molecular stuff of the chromosome, it must be able to reproduce itself.
- The DNA double helix rewinds and separates into two single strands (Fig. 1-6).
- As the unwinding occurs, the single strands act as templates for synthesis of new complementary strands.
- When the parent DNA double helix has completed its unwinding, two new DNA double-stranded molecules are formed.
- The process by which new DNA is formed is called *replication*.

Protein Synthesis

How can proteins be synthesized in cells?

- The order of the N bases on the DNA molecule determines the order of amino acids in the protein molecule.
- While DNA is in the nucleus, the proteins are synthesized on ribosomes outside the nucleus as follows:

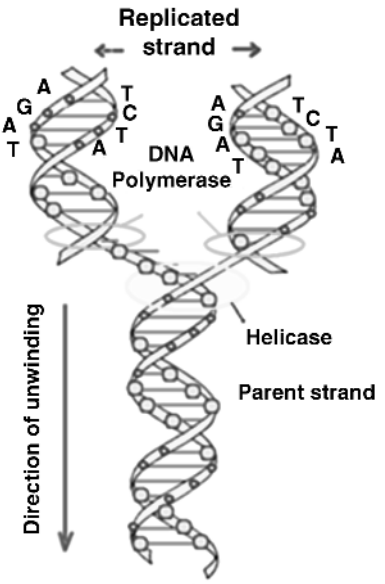


FIGURE 1-6 DNA double helix rewinds and separates into two single strands.

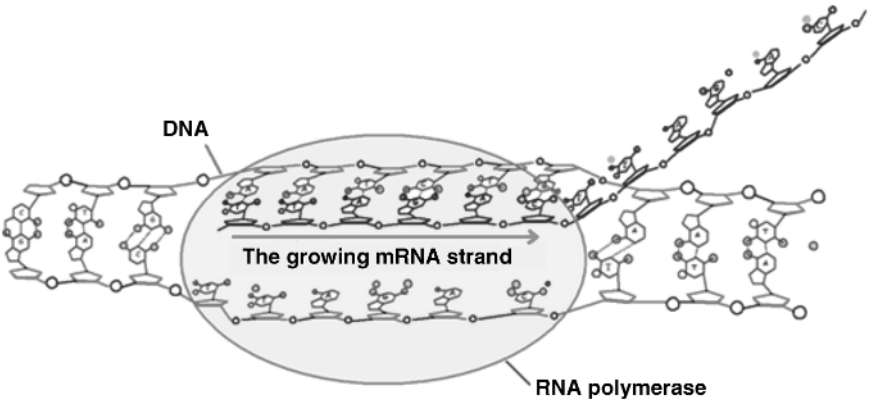
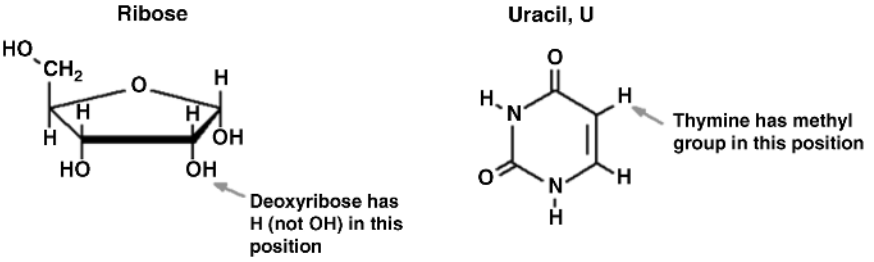


FIGURE 1-7 Synthesis of mRNA.

- As the DNA double helix unwinds, the N base segment becomes exposed.
- The DNA molecule serves as template for the synthesis of *mRNA* molecule.
- The synthesis of mRNA is analogous to the replication synthesis of DNA (Fig. 1-7).
- mRNA has structure similar to DNA but contains:
  - Ribose instead of deoxyribose
  - N-base uracil instead of thymine:



- After mRNA is synthesized, it is transported out of the nucleus and becomes attached to the ribosomes, where the protein syntheses begin (Fig. 1-8).
- At the ribosomes, the order of the bases on the mRNA determines the amino acid sequence in the protein molecule.
- The amino acid sequence is determined by a triplet code on the mRNA molecule.
- A group of three N bases represents a code for signifying a single amino acid (Scheme 1-2).
- The amino acids are brought to the mRNA at the ribosomes by much smaller RNA molecules called *tRNA*.
- Each tRNA has a triplet of bases, which is complementary to an amino acid code on mRNA.
- The tRNA molecules bring the amino acids to the ribosomes as they move along the mRNA strand, and the amino acids are knit into the growing protein chain.

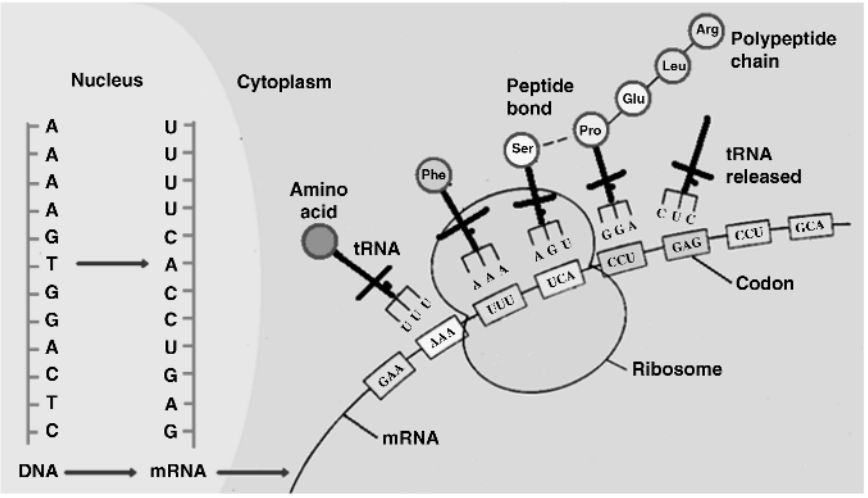


FIGURE 1-8 Protein synthesis.

- After the tRNA has discharged its amino acid passenger, it moves out into the cytoplasm, finds another amino acid, and returns to the ribosome surface.

Common Natural α-Amino Acids

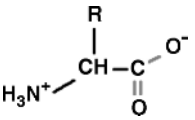
Give the general formula, side chain, and corresponding name of the common natural α -amino acids.

- There are 20 common natural amino acids.

Gly :	GGU, GGC, GGA, GGG	Met :	AUA, AUG
Ala :	GCU, GCC, GCA, GCG	Tyr :	UAU, UAC
Val :	GUU, GUC, GCA, GUG	Asp :	GAU, GAC
Arg :	CGU, CGC, CGA, CGG	Asn :	AAU, AAC
Pro :	CCU, CCC, CCA, CCG	Glu :	GAA, GAU
Ser :	UCU, UCC, UCA, UCG	Gln :	CAA, CAG
Thr :	ACU, ACC, ACA, ACG	His :	CAU, CAC
Leu :	CUU, CUC, CUA, CUG	Lys :	AAA, AAG
Leu :	UUA, UUG	Phe :	UUU, UUC
Ile :	AUU, AUC	Arg :	AGA, AGG
Ser :	AGU, AGC	Chain termination :	UAA, UAG
Cys :	UGU, UGC		

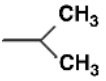
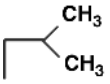
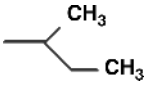
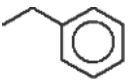
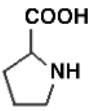
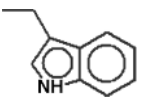
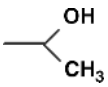
SCHEME 1-2 Genetic codes.

- The general formula for an α-amino acids is



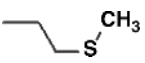
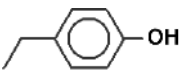
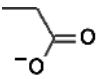
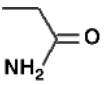
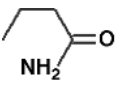
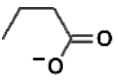
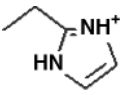
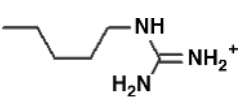
- They are summarized in Table 1-5.

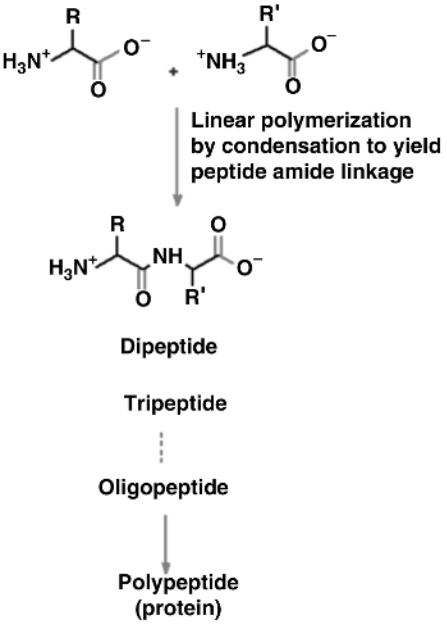
TABLE 1-5 L-α-amino Acids

Name	Side Chain (R at pH = 7)	pK_a	Nature
Glycine, Gly, G	—H	2.35, 9.78	Structural, spacer
Alanine, Ala, A	—CH_3	2.35, 9.87	Hydrophobic
Valine, Val, V		2.29, 9.74	Hydrophobic
Leucine, Leu, L		2.33, 9.74	Hydrophobic
Isoluecine, Ile, I		2.32, 9.76	Hydrophobic
Phenylalanine, Phe, F		2.16, 9.18	Hydrophobic
Proline, Pro, P		1.95, 10.64	Hydrophobic, structural
Tryptophan, Trp, W		2.43, 9.44	Hydrophobic
Serine, Ser, S		2.19, 9.21	Ambivalent
Threonine, Thr, T		2.09, 9.11	Hydrophobic

(*continued*)

Table 1-5 (*Continued*)

Name	Side Chain (R at pH = 7)	pK_a	Nature
Methionine, Met, M		2.13, 9.28	Hydrophobic but weak Lewis base, soft
Tyrosine, Tyr, T		~10	Hydrophobic, but strong Lewis base, only when deprotonated
Aspartic, Asp, D		~5	Hydrophobic, Lewis base, anion
Asparagine, Asn, N		2.1, 8.84	Lewis base, anion
Glutamine, Gln, Q		1.99, 3.90, 9.90	Polar, neutral
Glutamic, Glu, E		2.16, 4.27, 9.36	Lewis base, anion
Histidine, His, H		1.80, 6.04, 9.33	Hydrophobic, Lewis base
Cysteine, Cys, C		1.92, 8.35, 10.46	Lewis base, anion, soft
Lysine, Lys, K		2.16, 9.18, 10.79	Polar, cationic, protonated
Arginine, Arg, R		1.82, 8.99, 12.48	Polar, cationic, protonated



SCHEME 1-3 Polypeptide formation.

Peptide Chain Formation

How can the peptide chain be formed from the amino acids?

- Linear polymerization by condensation to yield amide peptide linkage (Scheme 1-3).
- All proteins are polypeptides.

Protein physiological functions

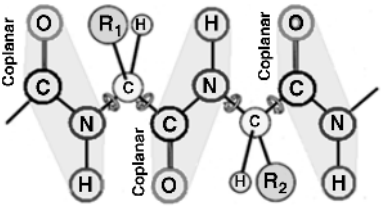
What are the physiological roles of proteins?

- The physiological roles of proteins are:
  - Structural: finger nails, hair, and skin
  - Transport: oxygen, electrons, and iron
  - Catalysis: enzymes responsible for all synthesis of proteins, DNA, and organics

Structural Features of Proteins

Define: primary, secondary, tertiary, and quaternary structures. And what are the factors that control each of these structures?

- The properties and functions of a particular protein depend on the sequence of the amino acids in the protein, or the *primary structure*.
  - The primary structure determines higher levels of structures.
  - These structural details are crucial to the biological role of a protein.
- The *secondary structure* arises from the relative disposition of atoms in the polypeptide "backbone":



The groups of four gray-shaded atoms are coplanar. Free rotation occurs about the bond connecting the carbon with the carbonyl and the nitrogen. Therefore, the extended polypeptide chain is a semirigid structure with two-thirds of the atoms of the backbone held in a fixed plane.

- Examples of secondary structures:
  (a) random coil
  (b) α–helix (Fig. 1-9)
  (c) β–pleated (Fig. 1-10), associated as (i) parallel and (ii) antiparallel
  (d) reverse turns (Fig. 1-11)
  (e) omega loops (Fig. 1-12)

Both reverse turns and omega loops appear at the outer surface of the molecules.

- *A Tertiary structure* refers to the folding of the already secondary structured amino acids to form a three-dimensional (3D) structure. The overall 3D architecture of the polypeptide backbone:
  - Fibrous proteins: coils (Fig. 1-13).
  - Globular proteins: compact, ellipsoidal, spherical, until denatured. The folded tertiary, globular, structure of myoglobins is imposed over the helical secondary structure. Structures from X-ray diffraction are shown in Fig. 1-14.
  - Synthetic polypeptides have random or simply repetitive structures.

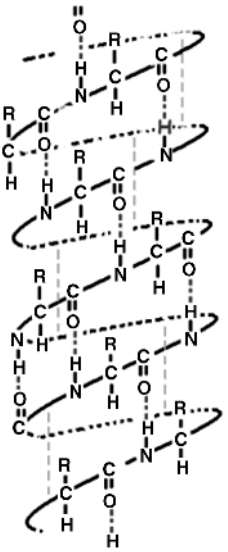


FIGURE 1-9 α-Helix structure of protein.

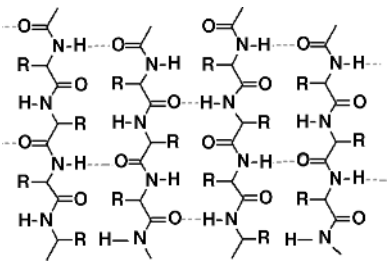


FIGURE 1-10 β-Pleated structure.

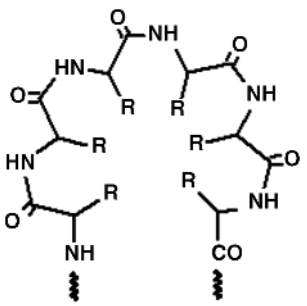


FIGURE 1-11 Reverse turn.

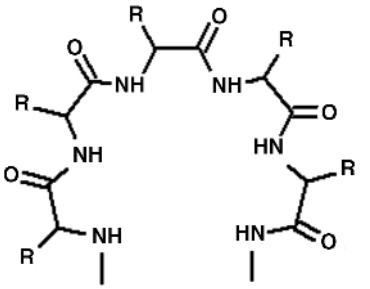


FIGURE 1-12 Omega loop.

FIGURE 1-13 Fibrous oligomers, PDB 1G6U (Ogihara et al., 2001).

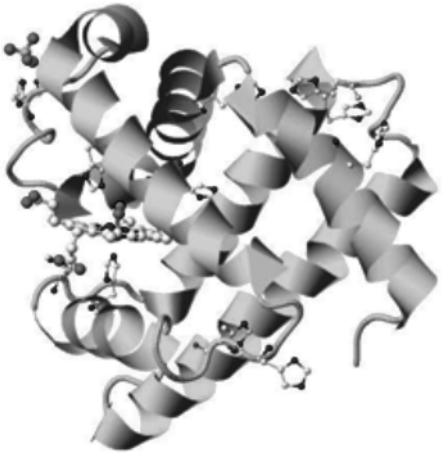


FIGURE 1-14 Tertiary structure of oxymyoglobin at 1.6 Å resolution, PDB 1MBO (Phillips, 1980).

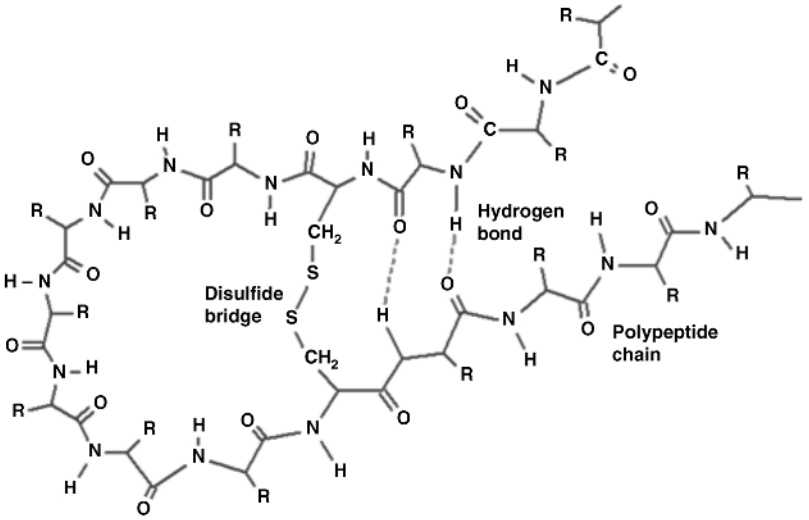


FIGURE 1-15 Disulfide linkages and H bonding.

Causes of Polypeptide Chain Folding

- Disulfide linkages (cysteine) (Fig. 1-15)
  - Disulfide linkage is a redox reaction:

$$R-S-S-R + 2H^+ + 2e^- \rightleftharpoons 2RSH$$

the standard redox potential, $E^{0'} = -0.40\ V$ for Cystine/Cysteine

  - To a large extent, various folding factors rely on "correct" positioning to relevant residues by other contributing folding factors, i.e., there is cooperativity, which causes an entropy gain.
- H-bonding
  - Hydrogen bonds within proteins are constant in time, whereas in fluid media, they are constantly breaking and re-forming.
  - Again, groups are in correct proximity (Fig. 1-15).
- A *hydrophobic interaction* arises from the unfavorable nature of interactions between water and nonpolar solutes (Fig. 1-16).
  - There is a common tertiary structure among proteins from diverse species. Similar folding conformations of distantly related cytochromes (Figs. 1-17 to 1-19) are noticed.
  - The interior packing is composed of generally dense, van Der Waals interactions, although voids are found (Scheme 1-4).

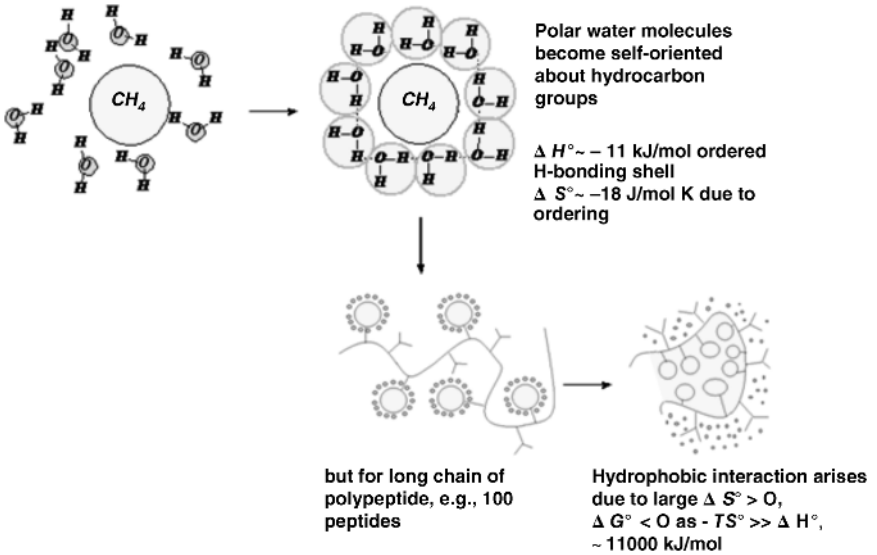


FIGURE 1-16 Hydrophobic interaction and solvent entropy.

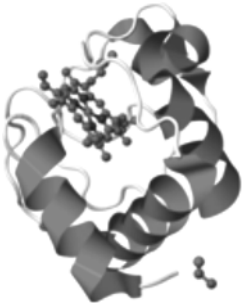


FIGURE 1-17 Cytochrome *c*, tuna, PDB 3CYT (Takano and Dickerson, 1980).

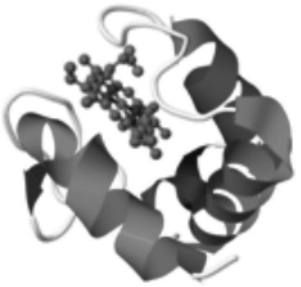


FIGURE 1-18 Cytochrome c_{553}, *Bacillus pasteurii*, PDB 1C75 (Benini et al., 2000).

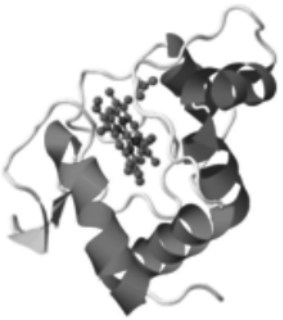
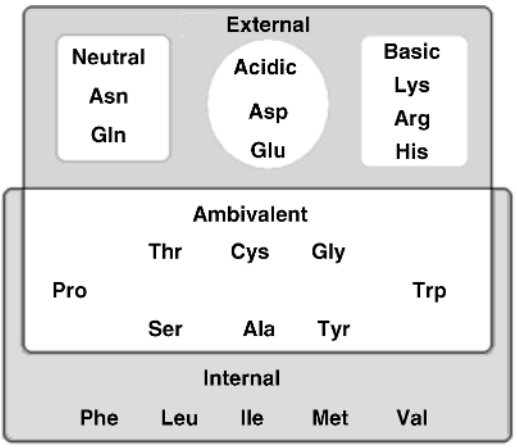


FIGURE 1-19 Cytochrome c_2, *Rhodobacter sphaeroides*, PDB 1CXC (Axelrod et al., 1994).

- Ionized groups occur:
  - (i) On the outer surface (majority, 100%)
  - (ii) In clefts or inner sites, where they have a particular/special role in the protein's function

- *Unfolding* is caused by:
  - (i) Conformational entropy—more orientations accessible
  - (ii) Strain in folded state
- *Quaternary structure* refers to the aggregation of polypeptide chains into larger assemblies such as in hemoglobin (Fig. 1-20), and hemerythrin. In hemerythrin

8He	$\rightleftarrows$	He_8
Subunits (13,500)		Octamer (108,000)



SCHEME 1-4 External, ambivalent, and internal amino acids.

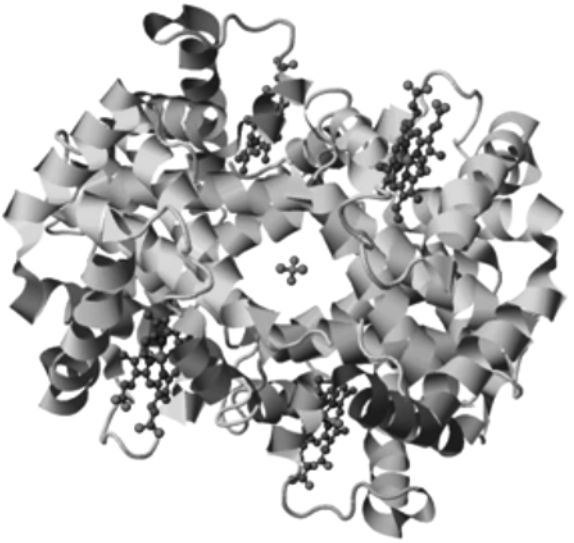


FIGURE 1-20 Quaternary structure of human oxyhemoglobin at 2.1 Å resolution, PDB 1HHO (Shaanan, 1983).

There are two types:

(i) Isologous: ⇆

(ii) ii. Heterologous: ⇉

- *Aggregation* is driven by:
  (i) Hydrogen bonding
  (ii) Hydrophobic interaction
  (iii) Salt bridges: Lys^+, Arg^+ vs. Glu^-, Asp^-

- Ionic moieties brought together, Coulombic attraction, so $\Delta H < 0$, solvent H_2O released, so $\Delta S > 0$. For example, the association of the four subunits of Hb_4 has Standard Gibbs free energy, $\Delta G^{\circ} = -60\,\text{kJ}, -15\,\text{kJ/subunit}$.

Metal Amino Acid Complexes

Arrange the binding stabilities of various metal ions toward different amino acids.

- M^{n+} binding group are:

$$\text{Less stable} \xrightarrow{\text{Met}^- \text{ Tyr}^- \text{ Glu}^- \text{ Asp}^- \text{His}} \text{More stable}$$

Define:

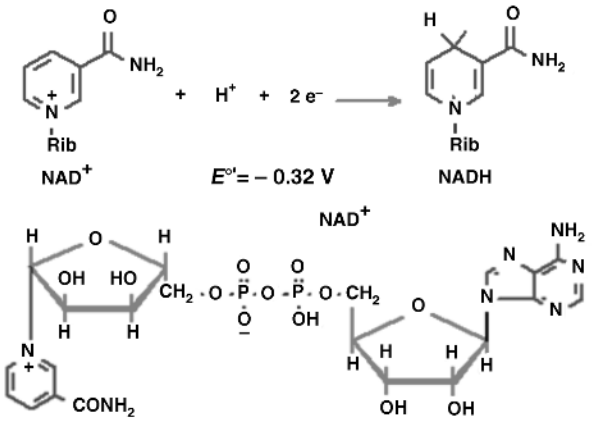
(a) Enzymes

(b) Metalloenzymes

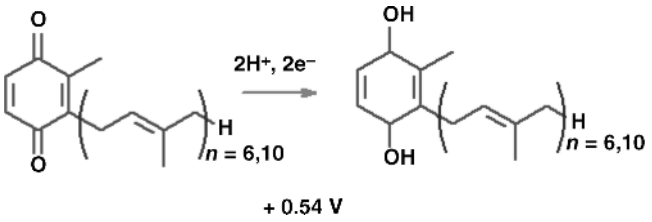
(c) Coenzymes

(d) Cofactors

- Enzymes:
  - Catalyze biological processes
  - Control rates of reactions
  - Promote certain geometries in the transition state, which lowers the activation energy for the formation of one product rather than the other
- *Matalloenzymes* are composed of:
  - A protein structure (called apoprotein/apoenzyme)
  - Small prosthetic group
  - Prosthetic groups that are a simple metal ion, a complex metal ion, or an organic compound
- *Coenzyme* reversibly combines with the enzyme for a particular reaction and then is released to combine with another.
- *Cofactors* are the prosthetic groups and the coenzymes.
  - Provide ability to *transfer* molecular groups or radicals that polypeptides cannot (e^-, phosphate, alkyl group, etc.), in enzyme-catalyzed reactions
  - Provide ability to *bind and transfer* molecules that polypeptide cannot (e^-, O_2)
  - Simple cofactors: Mg^{2+}, Fe^{2+}, Zn^{2+}, etc.
  - Several are nucleotide derivatives of ATP
    - (i) Nicotinamide adenine dinucleotide (NADH) (Scheme 1-5): a mild source of H^- as NADH. Note pervasive presence of phosphate ester links.
    - (ii) Ubiquinone (coenzyme-Q), CoQ_6, CoQ_{10} (Scheme 1-6).

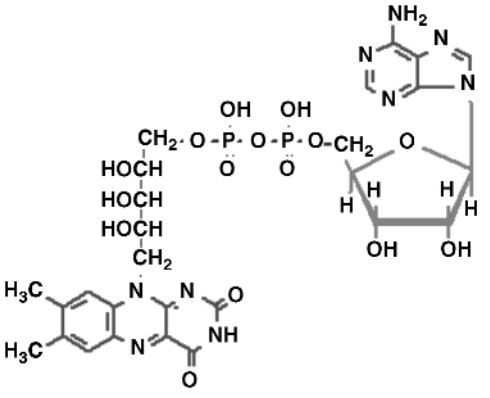


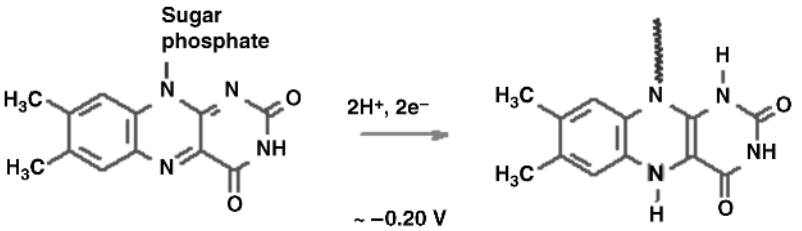
SCHEME 1-5 Nicotinamide adenine dinucleotide.



SCHEME 1-6 CoQ_6 and CoQ_{10}.

(iii) Flavins, i.e., flavin mononucleotide (FMN) (riboflavin phosphate) (Scheme 1-7):

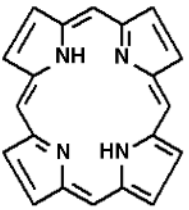


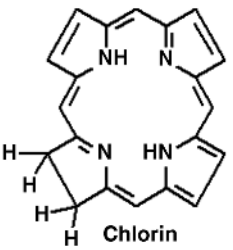


SCHEME 1-7 Flavin mononucleotide.

See also flavin adenine dinucleotide (FAD).

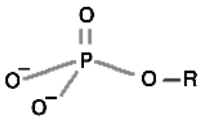
(iv) Tetrapyrrolic cofactors:





(v) Phosphates

- Suitable as noncarbon "universal" component
- Carbon-based esters subjected to hydrolysis by digestive enzymes
- Must be readily available in environment, so G° is not wasted in hunting and concentrating
- Used in presence of Cys–SH, so cannot be oxidized or reduced
- Used for persistent structures, so should be inert (slow reacting)
- Kinetic consideration:



P^{5+} used as ester

Rate of hydrolysis depends on rate of P–O bond scissions

Comparison of P–O versus M–O Bond Scission Rates for Row 3 Elements

Compare M–O bond scission rates for row-3 elements in group-oxidation states in H_2O, and show the advantages of P–O.

- Use O^{17}or O^{18} isotopes as tags [(e.g. O^{17}, nuclear magnetic resonance (NMR)]:

  - $t_{1/2}$ for O exchange at room temperature in seconds:

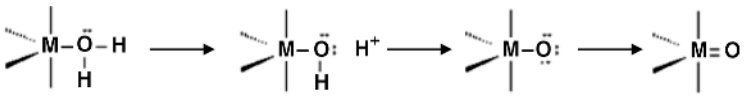
Na^+	Mg^{2+}	Al^{3+}	Si^{4+}	P^{5+}
10^{-9}	10^{-5}	10^{0}	10^{3}	10^{10}

    Therefore, phosphates are better than silicate.

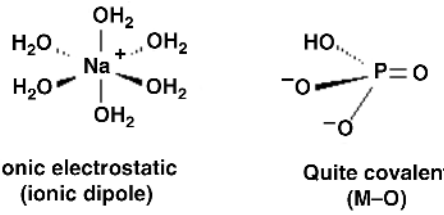
- Relative exchange rates: $Na^+ > Mg^{2+} > Al^{3+} > Si^{4+} > P^{5+}$

  → Slower
  → Size shrinks (r decreases)
  → Charge increases (q increases)

  - Exchange rates (↓) decrease as q/r (↑) increase as well as the ionic potential gets higher.
  - High ionic potential polarizes ligand, e.g., H_2O, and introduces covalency.



Consequently, H^+ is released, as increases of q/r lead to decreasing pK_a:



Redox Advantages: Sulfur versus Phosphorus

Consider all S and P possible anions, which will be the strongest oxidizing agent? And which will be the strongest reducing agent?

- Comparison of P and S:

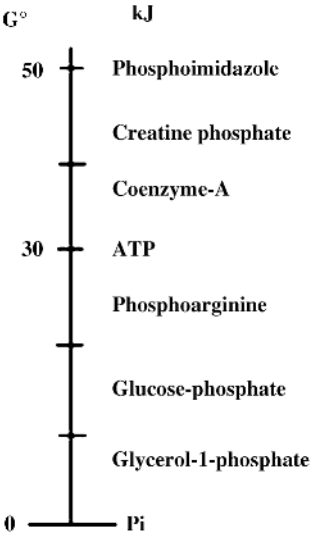
$2\ SO_4^{2-} + 4H^+ + e^-$	$\rightarrow$	$S_2O_6^{2-} + 2\ H_2O$	$E°\ (mV) = -220$
$S^{6+} + e^-$	$\rightarrow$	S^{5+}	
$2\ SO_3^{2-} + 4H^+ + 2e^-$	$\rightarrow$	$S_2O^{2-} + 2\ H_2O$	$E°\ (mV) = -86$
$S^{4+} + 2\ e^-$	$\rightarrow$	S^{2+}	
$S + 2H^+ + 2e^-$	$\rightarrow$	H_2S	$E°\ (mV) = +142$
$S^0 + 2\ e^-$	$\rightarrow$	S^{2-}	
$SO_4^{2-} + 2H^+ + 2e^-$	$\rightarrow$	$SO_3^{2-} + H_2O$	$E°\ (mV) = +172$
$cS^{6+} + 2e^-$	$\rightarrow$	S^{4+}	
$SO_4^{2-} + 8H^+ + 6e^-$	$\rightarrow$	$S + 4H_2O$	$E°\ (mV) = +35$
$S^{6+} + 6e^-$	$\rightarrow$	S^0	
$S_2O_6^{2-} + 4H^+ + 2e^-$	$\rightarrow$	$2\ SO_3^{-2} + 4H_2O$	$E°\ (mV) = +564$
$S^{5+} + 2e^-$	$\rightarrow$	S^{4+}	
$PO_3^{3-} + 2H^+ + 2e^-$	$\rightarrow$	$PO_2^{3-} + H_2O$	$E°\ (mV) = -499$
$P^{3+} + 2e^-$	$\rightarrow$	P^+	
$PO_2^{3-} + 4H^+ + e^-$	$\rightarrow$	$P + 2H_2O$	$E°\ (mV) = -508$
$P^+ + e^-$	$\rightarrow$	P^0	
$PO_4^{3-} + 2H^+ + 2e^-$	$\rightarrow$	$PO_3^{3-} + H_2O$	$E°\ (mV) = -276$
$P^{+5} + 2e^-$	$\rightarrow$	P^{3+}	
$P + 3H^+ + 3e^-$	$\rightarrow$	PH_3	$E°\ (mV) = -63$
$P^0 + 3e^-$	$\rightarrow$	P^{3-}	

- Hot, concentrated H_2SO_4 is a strong oxidizing agent; dilute H_2SO_4 is not an oxidizing acid.
  - SO_3^{2-}, sulfite ion is mild reducing agent
  - HSO_3^-, hydrogen sulfite ion is mild reducing agent
  - SO_4^{2-}, sulfate ion is oxidizing agent only in concentrated acid
- H_3PO_4, is not oxidizing agent
  - $H_2PO_3^-$, dihydrogen phosphite ion is reducing agent in H^+ or OH^-
  - HPO_3^{2-}, hydrogen phosphite ion is reducing agent in H^+ or OH^-

Bioenergetic Phosphate Derivatives

Give examples of the phosphate adducts that are bioenergetically important.

- Other PO_3^{3-} adducts are bioenergetically important:



- ATP acts as G – currency of bioenergetics:

$$ATP + H_2O + (Mg^{2+}) \rightarrow ADP + Pi \qquad \Delta G^\circ = 30\,kJ/mol$$

Corresponds to free energy available from transferring PO_3^- unit to H_2O.

REFERENCES

H. L. Axelrod, G. Feher, J. P. Allen, A. J. Chirino, M. W. Day, B. T. Hsu, and D. C. Rees, *Acta Crystallogr., Sect. D*, 50, 596–602 (1994).

S. Benini, A. Gonzalez, W. R. Rypniewski, K. S. Wilson, J. J. Van Beeumen, and S. Ciurli, *Biochemistry*, 39, 13115–13126 (2000).

F. A. Cotton and G. Wilkinson, in *Advanced Inorganic Chemistry*, 4th ed., Wiley, p. 1311, Hoboken, NJ (1980).

N. L. Ogihara, G. Ghirlanda, J. W. Bryson, M. Gingery, W. F. DeGrado, and D. Eisenberg, *Proc. Natl. Acad. Sci. USA*, 98, 1404–1409 (2001).

S. E. Phillips, *J. Mol. Biol.*, 142, 531–554 (1980).

B. Shaanan, *J. Mol. Biol.*, 171, 31–59 (1983).

T. Takano and R. Dickerson, *Proc. Natl. Acad. Sci. USA*, 77, 6371–6375 (1980).

SUGGESTIONS FOR FURTHER READING

Texts on Biochemistry

1. J. J. R. F. da Silva and R. J. P. Williams, *Biological Chemistry of Elements*, Oxford University Press, New York (1991).
2. L. Stryer, *Biochemistry*, Freeman, New York (1995).
3. D. Voet and J. G. Voet, *Biochemistry*, Wiley, New York (1995).

4. *Advances in Protein Chemistry*, Academic Press, New York.
5. P. D. Boyer, Ed., *The Enzymes*, 3rd ed., Academic, New York (1970–1986).
6. H. Neurath, Ed., *The Proteins*, 2nd ed., Academic, New York, vol. I to vol. V.

Texts on Bioinorganic Chemistry

7. I. Bertini, H. B. Gary, E. I. Stiefel, and J. S. Valentine, in *Biological Inorganic Chemistry*, University Science Books Sausalito, CA, (2007).
8. H-B. Kraatz and N. Metzler-Nolte, in *Concepts and Models in Bioinorganic Chemistry*, Wiley, Hoboken, NJ (2006).
9. W. Kaim and B. Schwederski, in *Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life*, Wiley, New York (1994).
10. E-I. Ochaia, in *Bioinorganic Chemistry: A Survey*, Elsevier, San Diego, CA (2008, 2011).
11. R. M. Roat-Malone, in *Bioinorganic Chemistry: A Short Course*, Wiley-Interscience, Hoboken, NJ (2002).
12. S. J. Lippard and J. M. Berg, in *Principles of Bioinorganic Chemistry*, University Science Books, Mill Valley, CA (1994).
13. L. Que, Jr., Ed., *Physical Methods in Bioinorganic Chemistry*, University Science Books, Mill Valley, CA (2001).
14. R. B. King, Ed., *Encyclopedia of Inorganic Chemistry*, Wiley, New York, (1994).
15. J. E. Macintyre, A. Exec. Ed., in *Dictionary of Inorganic Compounds*, Chapman and Hall, London (1992).
16. A. S. Brill, in *Transition Metals in Biochemistry in Molecular Biology, Biochemistry, and Biophysics*, A. Kleinzeller, G. F. Springer, and H. E. Wittman, Eds., Vol. 26, Springer-Verlag, Berlin (1977).
17. D. R. Williams, Ed., *An Introduction to Bio-Inorganic Chemistry*, C. C. Thomas, Springfield, IL (1976).
18. R. F. Gould, Ed., *Bioinorganic Chemistry*, ACS Advances in Chemistry Series No. 100; K. N. Raymond, Ed., *Bioinorganic Chemistry II*, ACS Advances in Chemistry Series No. 162, American Chemical Society, Washington, DC (1977).
19. A. W. Addison, W. R. Cullen, D. Dolphin, and B. R. James, Eds., *Biological Aspect of Inorganic Chemistry*, Wiley, New York (1977).
20. E. I. Ochiai, *Bioinorganic Chemistry: An Introduction*, Allyn and Bacon, Wiley, Rockleigh, Boston (1977).
21. H. Sigel, in *Metal Ion in Biological Systems*, Vols. 1–20, Marcel Dekker, Basel.
22. G. L. Eichhorn, Ed., *Inorganic Biochemistry*, Elsevier, Amsterdam (1973).
23. M. N. Hughes, in *The Inorganic Chemistry of Biological Process*, 2nd ed., Wiley, London (1981).
24. P. M. Harrison and R. J. Hoare, in *Metals in Biochemistry*, Chapman and Hall, London and New York (1980).
25. R. J. P. Williams and J. R. R. F. da Silva, in *New Trend in Bio-Inorganic Chemistry*, Academic, London (1978).
26. C. A. Mc Auliffe, Ed., *Techniques and Topic in Bioinorganic Chemistry*, Macmillan, London (1975).