## Introduction

This paperback atlas is intended for students of medicine and the biological sciences. It provides an introduction to biochemistry, but with its modular structure it can also be used as a reference book for more detailed information. The 216 color plates provide knowledge in the field of biochemistry, accompanied by detailed information in the text on the facing page. The degree of dif - culty of the subject-matter is indicated by symbols in the text:

- ● stands for "basic biochemical knowledge"
- ◑ indicates "standard biochemical knowledge"
- ○ means "specialist biochemical knowledge."

Some general rules used in the structure of the illustrations are summed up in two *explanatory plates* inside the front and back covers. Keywords, definitions, explanations of unfamiliar concepts and chemical formulas can be found using the *index*. The book starts with a few **basics** in biochemistry (pp. 2–33). There is a brief explanation of the concepts and principles of chemistry (pp. 2–15). These include the periodic table of the elements, chemical bonds, the general rules governing molecular structure, and the structures of important classes of compounds. Several basic concepts of *physical chemistry* are also essential for an understanding of biochemical processes. Pages 16–33 therefore discuss the various forms of energy and their interconversion, reaction kinetics and catalysis, the properties of water, acids and bases, and redox processes.

These basic concepts are followed by a section on the structure of the important biomolecules (pp. 34–87). This part of the book is arranged according to the different classes of metabolites. It discusses carbohydrates, lipids, amino acids, peptides and proteins, nucleotides, and nucleic acids.

The next part presents the reactions involved in the interconversion of these compounds—the part of biochemistry that is commonly referred to as **metabolism** (pp. 88–195). The section starts with a discussion of the enzymes and coenzymes, and discusses the mechanisms of metabolic regulation and the so-called *energy metabolism*. After this, the central metabolic pathways are presented, once again arranged according to the class of metabolite (pp. 150–195).

The second half of the book begins with a discussion of the functional compartments within the cell, the **cellular organelles** (pp. 196–235). This is followed on pp. 236–265 by the current field of **molecular genetics** (*molecular biology*). A further extensive section is devoted to the biochemistry of individual **tissues and organs** (pp. 266–359). Here, it has only been possible to focus on the most important organs and organ systems—the digestive system, blood, liver, kidneys, muscles, connective and supportive tissues, and the brain.

Other topics include the biochemistry of **nutrition** (pp. 360–369), the structure and function of important **hormones** (pp. 370–393), and **growth and development** (pp. 394–405).

The paperback atlas concludes with a series of schematic **metabolic "charts"** (pp. 407–419). These plates, which are not accompanied by explanatory text apart from a brief introduction on p. 406, show simplified versions of the most important synthetic and degradative pathways. The charts are mainly intended for reference, but they can also be used to review previously learned material. The enzymes catalyzing the various reactions are only indicated by their EC numbers. Their names can be found in the systematically arranged and annotated enzyme list (pp. 420–430).

## Periodic table

### A. Biologically important elements ◑

There are 81 stable elements in nature. Fifteen of these are present in all living things, and a further 8–10 are only found in particular organisms. The illustration shows the first half of the **periodic table**, containing all of the biologically important elements. In addition to physical and chemical data, it also provides information about the distribution of the elements in the living world and their abundance in the human body. The laws of atomic structure underlying the periodic table are discussed in chemistry textbooks.

More than 99% of the atoms in animals' bodies are accounted for by just four elements—hydrogen (H), oxygen (O), carbon (C) and nitrogen (N). Hydrogen and oxygen are the constituents of water, which alone makes up 60–70% of cell mass (see p. 196). Together with carbon and nitrogen, hydrogen and oxygen are also the major constituents of the **organic compounds** on which most living processes depend. Many biomolecules also contain sulfur (S) or phosphorus (P). The above **macroelements** are essential for all organisms.

A second biologically important group of elements, which together represent only about 0.5% of the body mass, are present almost exclusively in the form of **inorganic ions**. This group includes the *alkali metals* sodium (Na) and potassium (K), and the *alkaline earth metals* magnesium (Mg) and calcium (Ca). The halogen *chlorine* (Cl) is also always ionized in the cell. All other elements important for life are present in such small quantities that they are referred to as **trace elements**. These include transition metals such as iron (Fe), zinc (Zn), copper (Cu), cobalt (Co) and manganese (Mn). A few *nonmetals,* such as iodine (I) and selenium (Se), can also be classed as essential trace elements.

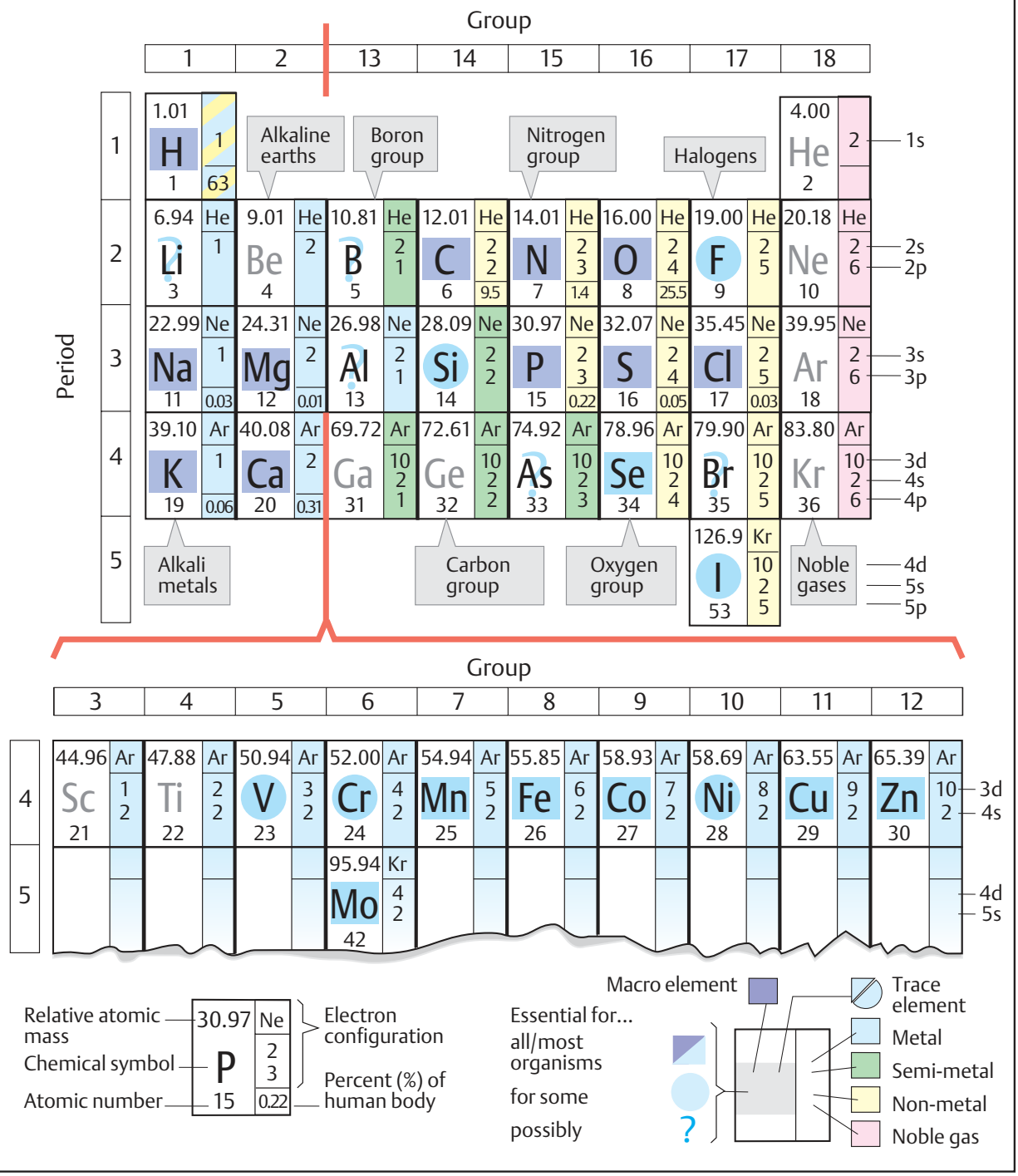
### B. Electron configurations: examples ○

The chemical properties of atoms and the types of bond they form with each other are determined by their electron shells. The **electron configurations** of the elements are therefore also shown in Fig. **A**. Fig. **B** explains the symbols and abbreviations used. More detailed discussions of the subject are available in chemistry textbooks.

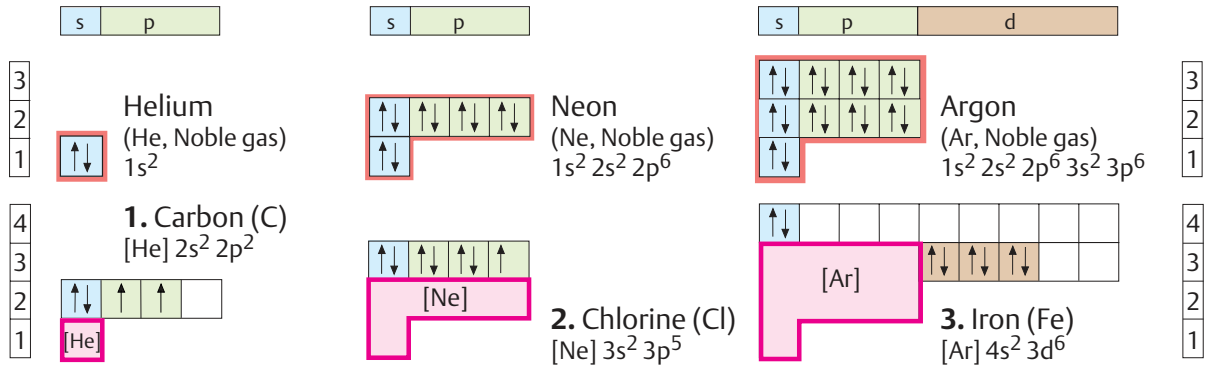
The possible states of electrons are called **orbitals**. These are indicated by what is known as the principal quantum number and by a letter—s, p, or d. The orbitals are filled one by one as the number of electrons increases. Each orbital can hold a maximum of two electrons, which must have oppositely directed "spins." Fig. **A** shows the distribution of the electrons among the orbitals for each of the elements. For example, the six electrons of carbon (**B1**) occupy the 1s orbital, the 2s orbital, and two 2p orbitals. A filled 1s orbital has the same electron configuration as the noble gas helium (He). This region of the electron shell of carbon is therefore abbreviated as "He" in Fig. **A**. Below this, the numbers of electrons in each of the other filled orbitals (2s and 2p in the case of carbon) are shown on the right margin. For example, the electron shell of chlorine (**B2**) consists of that of neon (Ne) and seven additional electrons in 3s and 3p orbitals. In iron (**B3**), a transition metal of the first series, electrons occupy the 4s orbital even though the 3d orbitals are still partly empty. Many reactions of the transition metals involve empty d orbitals—e. g., redox reactions or the formation of complexes with bases.

Particularly stable electron arrangements arise when the outermost shell is fully occupied with eight electrons (the "**octet rule**"). This applies, for example, to the noble gases, as well as to ions such as $Cl^-$ ($3s^2 3p^6$) and $Na^+$ ($2s^2 2p^6$). It is only in the cases of hydrogen and helium that two electrons are already suf cient to fill the outermost 1s orbital.

## A. Biologically important elements




## B. Electron configurations: examples



## Bonds

### A. Orbital hybridization and chemical bonding ○

Stable, covalent bonds between nonmetal atoms are produced when orbitals (see p. 2) of the two atoms form **molecular orbitals** that are occupied by one electron from each of the atoms. Thus, the four bonding electrons of the carbon atom occupy 2s and 2p atomic orbitals (**1a**). The 2s orbital is spherical in shape, while the three 2p orbitals are shaped like dumbbells arranged along the x, y, and z axes. It might therefore be assumed that carbon atoms should form at least *two different* types of molecular orbital. However, this is not normally the case. The reason is an effect known as **orbital hybridization**. Combination of the s orbital and the three p orbitals of carbon gives rise to four equivalent, tetrahedrally arranged $sp^3$ atomic orbitals (**$sp^3$ hybridization**). When these overlap with the 1s orbitals of H atoms, four equivalent σ-molecular orbitals (**1b**) are formed. For this reason, carbon is capable of forming four bonds—i. e., it has a valency of four. Single bonds between nonmetal atoms arise in the same way as the four σ or **single bonds** in methane ($CH_4$). For example, the hydrogen phosphate ion ($HPO_4^{2-}$) and the ammonium ion ($NH_4^+$) are also tetrahedral in structure (**1c**).

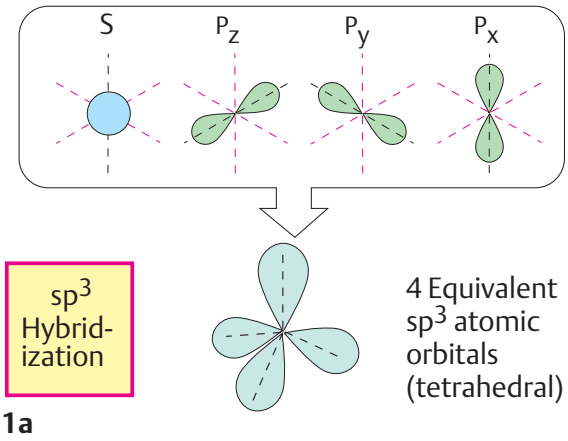
A second common type of orbital hybridization involves the 2s orbital and only *two* of the three 2p orbitals (2a). This process is therefore referred to as **$sp^2$ hybridization**. The result is three equivalent $sp^2$ hybrid orbitals lying in one plane at an angle of 120° to one another. The remaining $2p_x$ orbital is oriented perpendicular to this plane. In contrast to their $sp^3$ counterparts, $sp^2$-hybridized atoms form two *different* types of bond when they combine into molecular orbitals (**2b**). The three $sp^2$ orbitals enter into σ bonds, as described above. In addition, the electrons in the two $2p_x$ orbitals, known as **π electrons**, combine to give an additional, elongated π molecular orbital, which is located above and below the plane of the σ bonds. Bonds of this type are called **double bonds**. They consist of a σ bond and a π bond, and arise only when both of the atoms involved are capable of $sp^2$ hybridization. In contrast to single bonds, double bonds are not freely rotatable, since rotation would distort the π-molecular orbital. This is why all of the atoms lie in one plane (**2c**); in addition, *cis–trans* isomerism arises in such cases (see p. 8). Double bonds that are common in biomolecules are C=C and C=O. C=N double bonds are found in aldimines (Schiff bases, see p. 178).

### B. Resonance ◑

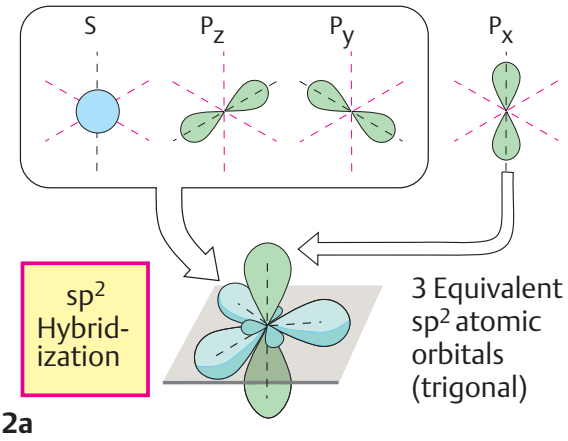
Many molecules that have several double bonds are much less reactive than might be expected. The reason for this is that the double bonds in these structures cannot be localized unequivocally. Their π orbitals are not confined to the space between the double-bonded atoms, but form a shared, extended **π-molecular orbital**. Structures with this property are referred to as **resonance hybrids**, because it is impossible to describe their actual bonding structure using standard formulas. One can either use what are known as **resonance structures**—i. e., idealized configurations in which π electrons are assigned to specific atoms (cf. pp. 32 and 66, for example)—or one can use dashed lines as in Fig. **B** to suggest the extent of the delocalized orbitals. (Details are discussed in chemistry textbooks.)

Resonance-stabilized systems include carboxylate groups, as in *formate*; aliphatic hydrocarbons with conjugated double bonds, such as *1,3-butadiene*; and the systems known as **aromatic ring systems**. The best-known aromatic compound is *benzene,* which has six delocalized π electrons in its ring. Extended resonance systems with 10 or more π electrons absorb light within the visible spectrum and are therefore *colored.* This group includes the aliphatic carotenoids (see p. 132), for example, as well as the heme group, in which 18 π electrons occupy an extended molecular orbital (see p. 106).

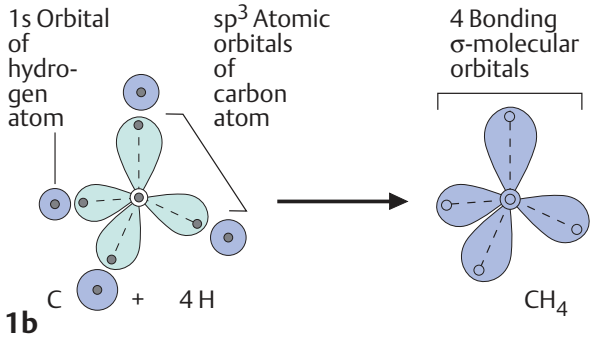
## A. Orbital hybridization and chemical bonding



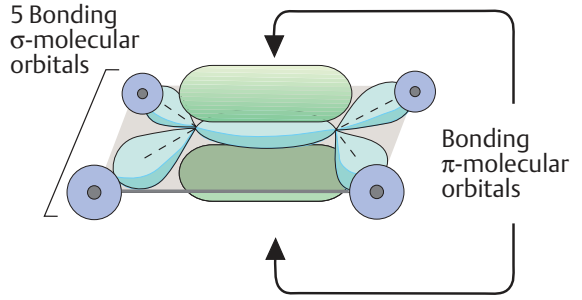

1a



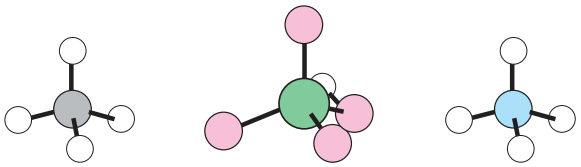

2a

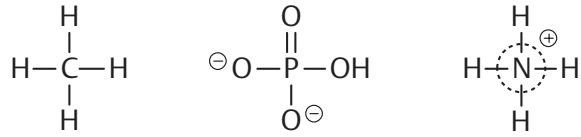



1b

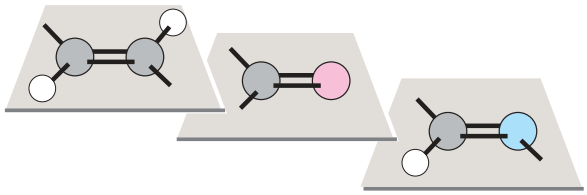


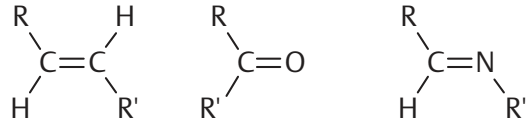

2b



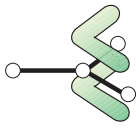
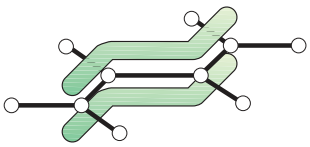
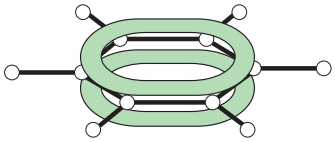
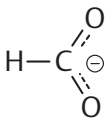
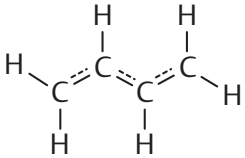
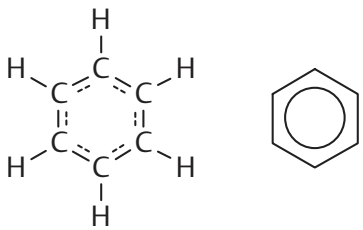
1c



2c

## B. Resonance

| | Formate | 1,3-Butadiene | Benzene |
|---|---|---|---|
| π-Molecular orbitals |  |  |  |
| Formula |  |  |  |

## Molecular structure

The physical and chemical behavior of molecules is largely determined by their **constitution** (the type and number of the atoms they contain and their bonding). Structural formulas can therefore be used to predict not only the chemical reactivity of a molecule, but also its size and shape, and to some extent its conformation (the spatial arrangement of the atoms). Some data providing the basis for such predictions are summarized here and on the facing page. In addition, L-dihydroxyphenylalanine (L-dopa; see p. 352), is used as an example to show the way in which molecules are illustrated in this book.

### A. Molecule illustrations ◑

In traditional two-dimensional **structural formulas** (**A1**), atoms are represented as letter symbols and electron *pairs* are shown as lines. Lines between two atomic symbols symbolize two **bonding electrons** (see p. 4), and all of the other lines represent **free electron pairs**, such as those that occur in O and N atoms. Free electrons are usually not represented explicitly (and this is the convention used in this book as well). Dashed or continuous circles or arcs are used to emphasize delocalized electrons.

**Ball-and-stick models** (**A2**) are used to illustrate the spatial structure of molecules. Atoms are represented as colored balls (for the color coding, see the inside front cover) and bonds (including multiple bonds) as gray cylinders. Although the relative bond lengths and angles correspond to actual conditions, the size at which the atoms are represented is too small to make the model more comprehensible.

Space-filling **van der Waals models** (**A3**) are useful for illustrating the actual shape and size of molecules. These models represent atoms as truncated balls. Their effective extent is determined by what is known as the van der Waals radius. This is calculated from the energetically most favorable distance between atoms that are not chemically bonded to one another.

### B. Bond lengths and angles ○

Atomic radii and distances are now usually expressed in picometers (pm; 1 pm = $10^{-12}$ m). The old angstrom unit (Å, Å = 100 pm) is now obsolete. The length of single bonds approximately corresponds to the sum of what are known as the **covalent radii** of the atoms involved (see inside front cover). Double bonds are around 10–20% shorter than single bonds. In $sp^3$-hybridized atoms, the angle between the individual bonds is approx. 110°; in $sp^2$-hybridized atoms it is approx. 120°.

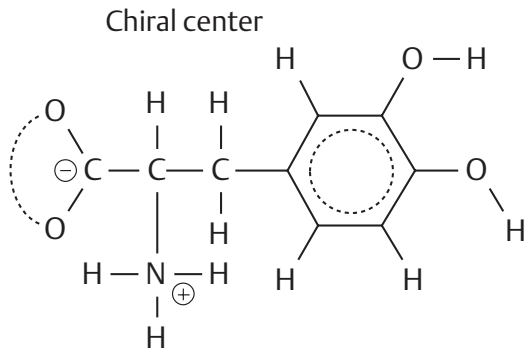
### C. Bond polarity ○

Depending on the position of the element in the periodic table (see p. 2), atoms have different **electronegativity**—i. e., a different tendency to take up extra electrons. The values given in **C2** are on a scale between 2 and 4. The higher the value, the more electronegative the atom. When two atoms with very different electronegativities are bound to one another, the bonding electrons are drawn toward the more electronegative atom, and the **bond** is **polarized**. The atoms involved then carry positive or negative partial charges. In **C1**, the van der Waals surface is colored according to the different charge conditions (red = negative, blue = positive). Oxygen is the most strongly electronegative of the biochemically important elements, with C=O double bonds being especially highly polar.

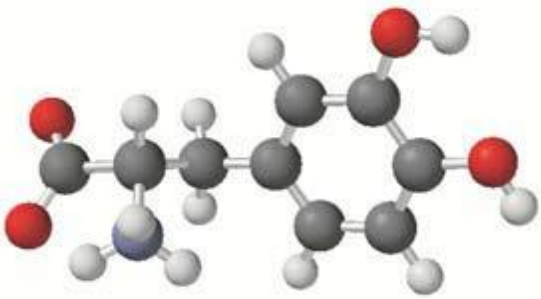
### D. Hydrogen bonds ◑

The **hydrogen bond**, a special type of noncovalent bond, is extremely important in biochemistry. In this type of bond, hydrogen atoms of OH, NH, or SH groups (known as hydrogen bond **donors**) interact with free electrons of **acceptor** atoms (for example, O, N, or S). The bonding energies of hydrogen bonds (10–40 kJ $mol^{-1}$) are much lower than those of covalent bonds (approx. 400 kJ $mol^{-1}$). However, as hydrogen bonds can be very numerous in proteins and DNA, they play a key role in the stabilization of these molecules (see pp. 68, 84). The importance of hydrogen bonds for the properties of water is discussed on p. 26.

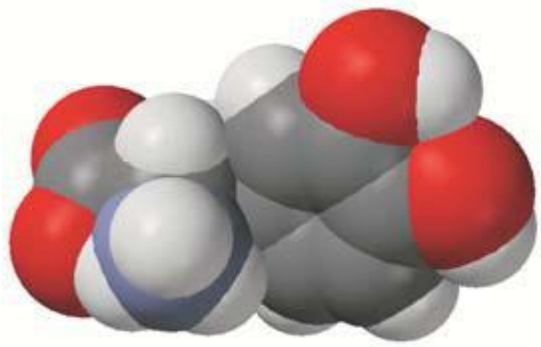
## A. Molecule illustrations




**1.** Formula illustration

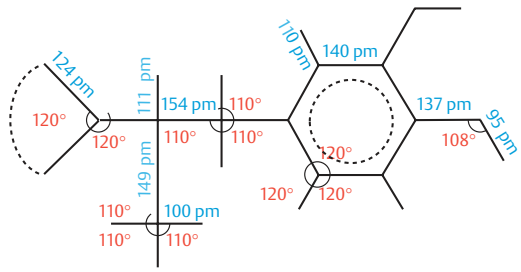


**2.** Ball- and-stick model

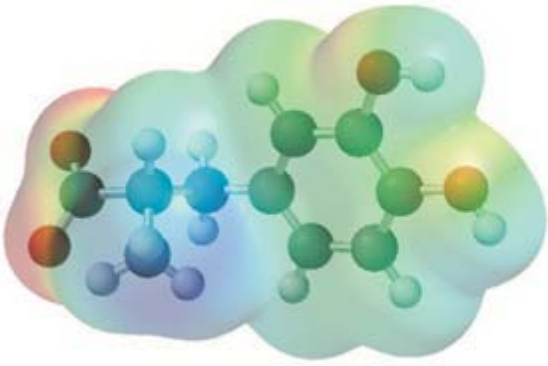


**3.** Van der Waals model

## B. Bond lengths and angles

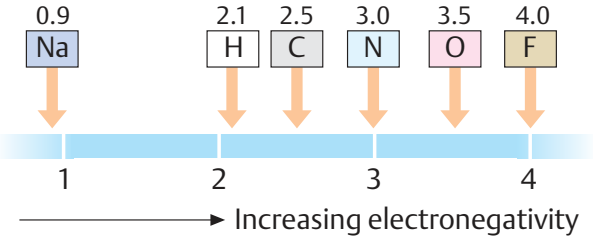



## C. Bond polarity



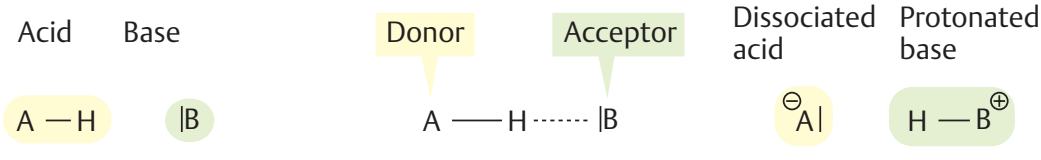
Positive Neutral Negative

**1.** Partial charges in L-dopa

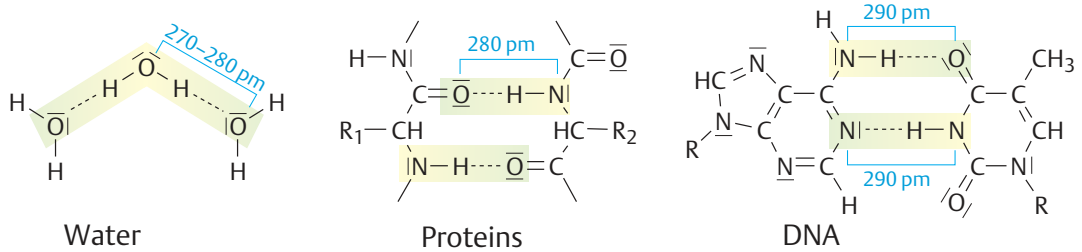



**2.** Electronegativities

## D. Hydrogen bonds




**1.** Principle




**2.** Examples

## Isomerism

Isomers are molecules with the same composition (i.e. the same molecular formula), but with different chemical and physical properties. If isomers differ in the way in which their atoms are bonded in the molecule, they are described as **structural isomers** (cf. citric acid and isocitric acid, **D**). Other forms of isomerism are based on different arrangements of the substituents of bonds (**A**, **B**) or on the presence of chiral centers in the molecule (**C**).

### *A. cis–trans* isomers ◑

Double bonds *are not freely rotatable* (see p. 4). If double-bonded atoms have different substituents, there are two possible orientations for these groups. In **fumaric acid**, an intermediate of the tricarboxylic acid cycle (see p. 136), the carboxy groups lie on *different* sides of the double bond (*trans* or *E* position). In its isomer **maleic acid**, which is not produced in metabolic processes, the carboxy groups lie on the *same* side of the bond (*cis* or *Z* position). *Cis–trans* isomers (**geometric isomers**) have different chemical and physical properties—e.g., their melting points (Fp.) and $pK_a$ values. They can only be interconverted by chemical reactions.

In lipid metabolism, *cis–trans* isomerism is particularly important. For example, double bonds in natural fatty acids (see p. 48) usually have a *cis* configuration. By contrast, unsaturated intermediates of β oxidation have a *trans* configuration. This makes the breakdown of unsaturated fatty acids more complicated (see p. 166). Light-induced *cis–trans* isomerization of retinal is of central importance in the visual cycle (see p. 358).

### B. Conformation ◑

Molecular forms that arise as a result of rotation around freely rotatable bonds are known as **conformers**. Even small molecules can have different conformations in solution. In the two conformations of **succinic acid** illustrated opposite, the atoms are arranged in a similar way to fumaric acid and maleic acid. Both forms are possible, although conformation 1 is more favorable due to the greater distance between the COOH groups and therefore occurs more frequently. Biologically active macromolecules such as proteins or nucleic acids usually have well-defined ("native") conformations, which are stabilized by interactions in the molecule (see p. 74).

### C. Optical isomers ◑

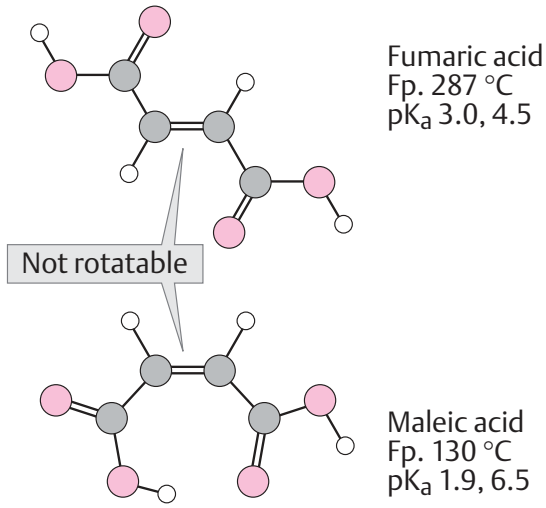
Another type of isomerism arises when a molecule contains a **chiral center** or is chiral as a whole. Chirality (from the Greek *cheir,* hand) leads to the appearance of structures that behave like image and mirror-image and that cannot be superimposed ("mirror" isomers). The most frequent cause of chiral behavior is the presence of an asymmetric C atom—i.e., an atom with four *different* substituents. Then there are two forms **(enantiomers)** with different **configurations.** Usually, the two enantiomers of a molecule are designated as L and D forms. Clear classification of the configuration is made possible by the *R/S system* (see chemistry textbooks).

Enantiomers have very similar chemical properties, but they rotate polarized light in opposite directions (**optical activity**, see pp. 36, 58). The same applies to the enantiomers of **lactic acid**. The dextrorotatory L-lactic acid occurs in animal muscle and blood, while the D form produced by microorganisms is found in milk products, for example (see p. 148). The Fischer projection is often used to represent the formulas for chiral centers (cf. p. 58).

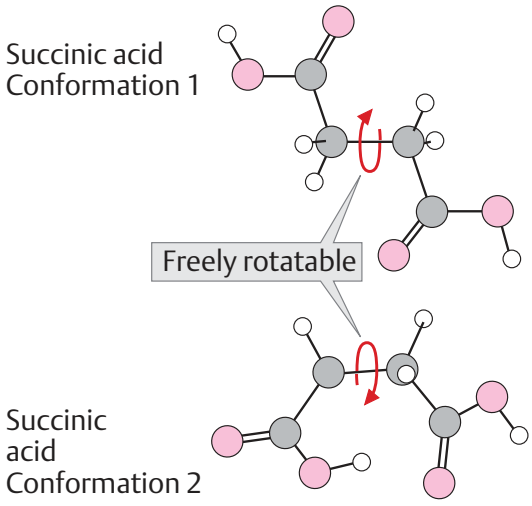
### D. The aconitase reaction ○

Enzymes usually function *stereospecifically.* In chiral substrates, they only accept one of the enantiomers, and the reaction products are usually also sterically uniform. *Aconitate hydratase* (aconitase) catalyzes the conversion of citric acid into the constitution isomer isocitric acid (see p. 136). Although citric acid is not chiral, aconitase only forms one of the four possible isomeric forms of isocitric acid (*2R,3S*-isocitric acid). The intermediate of the reaction, the unsaturated tricarboxylic acid *aconitate,* only occurs in the *cis* form in the reaction. The *trans* form of aconitate is found as a constituent of certain plants.

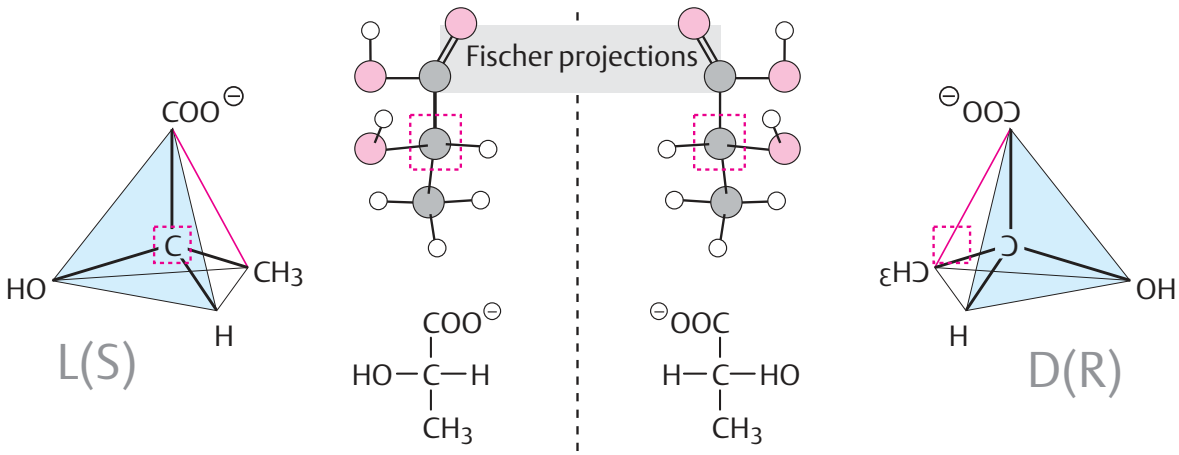
## A. *cis–trans* isomers



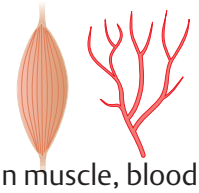

## B. Conformers




## C. Optical isomers




| | L-lactic acid |
|---|---|
| Fp. | 53 °C |
| pKa value | 3.7 |
| Specific rotation | + 2.5° |

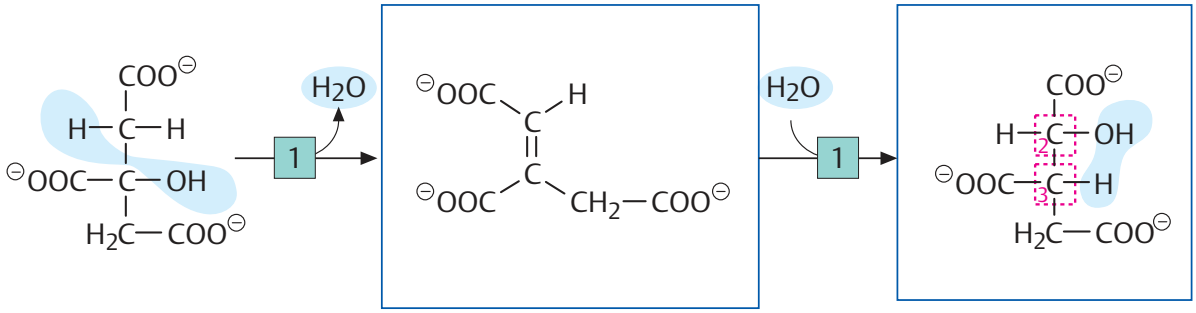


In muscle, blood

In milk products

| D-lactic acid | |
|---|---|
| 53 °C | Fp. |
| 3.7 | pKa value |
| -2.5° | Specific rotation |

## D. The aconitase reaction




Citrate (prochiral)

*cis*-Aconitate (intermediate product)

(*2R,3S*)-Isocitrate

*trans*-Aconitate occurs in plants

1 Aconitase *4.2.1.3*

## Biomolecules I

### A. Important classes of compounds ●

Most biomolecules are derivatives of simple compounds of the non-metals oxygen (O), hydrogen (H), nitrogen (N), sulfur (S), and phosphorus (P). The biochemically important oxygen, nitrogen, and sulfur compounds can be formally derived from their compounds with hydrogen (i.e., $H_2O$, $NH_3$, and $H_2S$). In biological systems, phosphorus is found almost exclusively in derivatives of phosphoric acid, $H_3PO_4$.

If one or more of the hydrogen atoms of a non-metal hydride are replaced formally with another group, R—e.g., alkyl residues—then derived compounds of the type R-$XH_{n-1}$, R-$XH_{n-2}$-R, etc., are obtained. In this way, **alcohols** (R-OH) and **ethers** (R-O-R) are derived from water ($H_2O$); primary **amines** (R-$NH_2$), secondary amines (R-NH-R) and tertiary amines (R-N-R′R″) amines are obtained from ammonia ($NH_3$); and **thiols** (R-SH) and **thioethers** (R-S-R′) arise from hydrogen sulfide ($H_2S$). Polar groups such as -OH and -$NH_2$ are found as substituents in many organic compounds. As such groups are much more reactive than the hydrocarbon structures to which they are attached, they are referred to as **functional groups**.

New functional groups can arise as a result of **oxidation** of the compounds mentioned above. For example, the oxidation of a thiol yields a **disulfide** (R-S-S-R). Double oxidation of a primary alcohol (R-$CH_2$-OH) gives rise initially to an **aldehyde** (R-C(O)-H), and then to a **carboxylic acid** (R-C(O)-OH). In contrast, the oxidation of a secondary alcohol yields a **ketone** (R-C(O)-R). The carbonyl group (C=O) is characteristic of aldehydes and ketones.

The addition of an amine to the carbonyl group of an aldehyde yields—after removal of water—an **aldimine** (not shown; see p. 178). Aldimines are intermediates in amino acid metabolism (see p. 178) and serve to bond aldehydes to amino groups in proteins (see p. 62, for example). The addition of an alcohol to the carbonyl group of an aldehyde yields a **hemiacetal** (R-O-C(H)OH-R). The cyclic forms of sugars are well-known examples of hemiacetals (see p. 36). The oxidation of hemiacetals produces carboxylic acid esters.

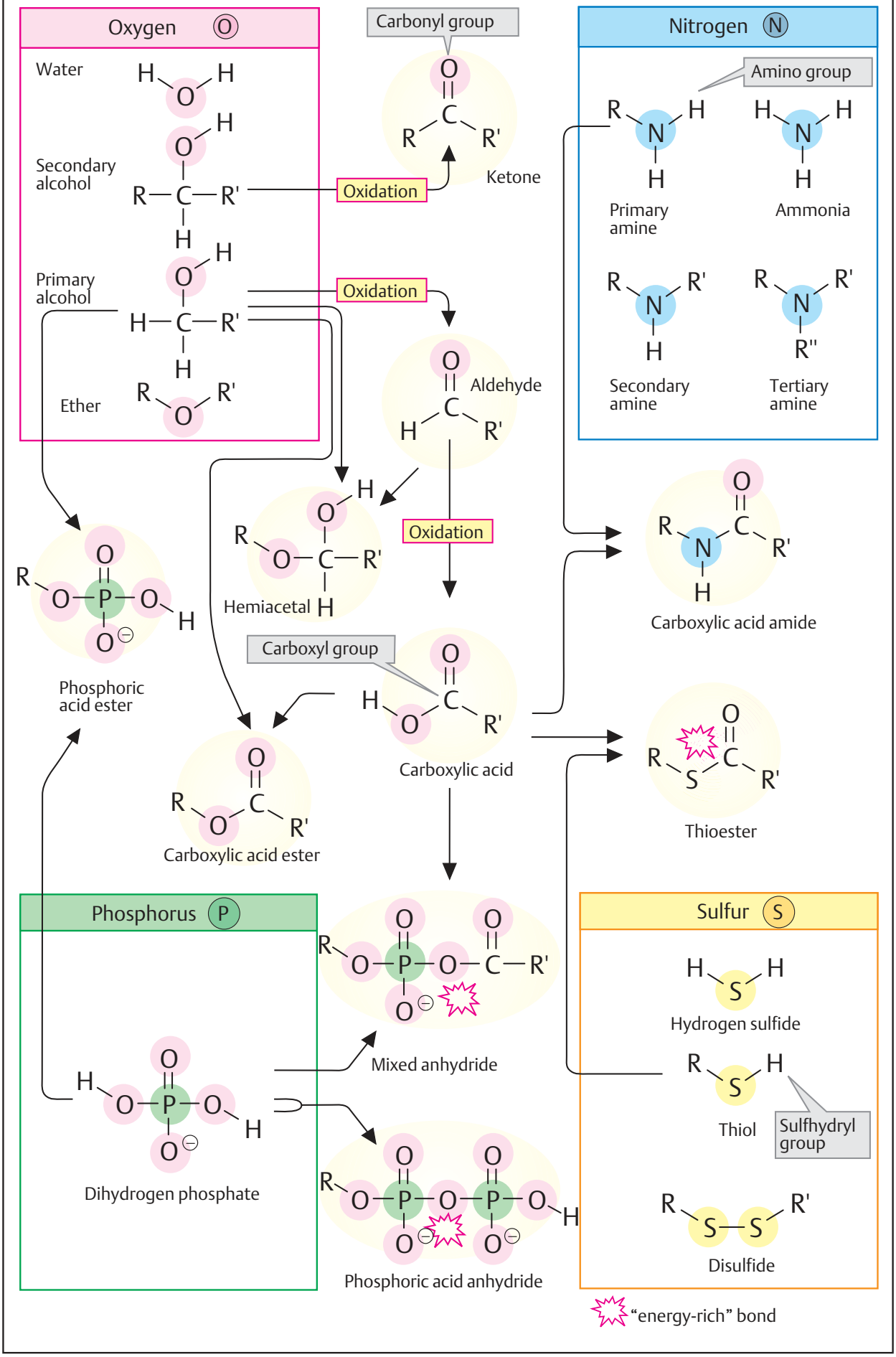
Very important compounds are the **carboxylic acids** and their derivatives, which can be formally obtained by exchanging the OH group for another group. In fact, derivatives of this type are formed by nucleophilic substitutions of activated intermediate compounds and the release of water (see p. 14). **Carboxylic acid esters** (R-O-CO-R′) arise from carboxylic acids and alcohols. This group includes the fats, for example (see p. 48). Similarly, a carboxylic acid and a thiol yield a **thioester** (R-S-CO-R′). Thioesters play an extremely important role in carboxylic acid metabolism. The best-known compound of this type is acetyl-coenzyme A (see p. 12).

Carboxylic acids and primary amines react to form **carboxylic acid amides** (R-NH-CO-R′). The amino acid constituents of peptides and proteins are linked by carboxylic acid amide bonds, which are therefore also known as peptide bonds (see p. 66).

Phosphoric acid, $H_3PO_4$, is a tribasic (triprotic) acid—i.e., it contains three hydroxyl groups able to donate $H^+$ ions. At least one of these three groups is fully dissociated under normal physiological conditions, while the other two can react with alcohols. The resulting products are phosphoric acid monoesters (R-O-P(O)O-OH) and diesters (R-O-P(O)O-O-R′). **Phosphoric acid monoesters** are found in carbohydrate metabolism, for example (see p. 36), whereas **phosphoric acid diester** bonds occur in phospholipids (see p. 50) and nucleic acids (see p. 82 ).

Compounds of one acid with another are referred to as **acid anhydrides**. A particularly large amount of energy is required for the formation of an acid—anhydride bond. Phosphoric anhydride bonds therefore play a central role in the storage and release of chemical energy in the cell (see p. 122). Mixed anhydrides between carboxylic acids and phosphoric acid are also very important "energy-rich metabolites" in cellular metabolism.

## A. Important classes of compounds



## Biomolecules II

Many biomolecules are made up of smaller units in a modular fashion, and they can be broken down into these units again. The construction of these molecules usually takes place through condensation reactions involving the removal of water. Conversely, their breakdown functions in a hydrolytic fashion—i.e., as a result of water uptake. The page opposite illustrates this modular principle using the example of an important coenzyme.

### A. Acetyl CoA ◑

Coenzyme A (see also p. 106) is a nucleotide with a complex structure (see p. 80). It serves to activate residues of carboxylic acids (acyl residues). Bonding of the carboxy group of the carboxylic acid with the thiol group of the coenzyme creates a **thioester bond** (-S-CO-R; see p. 10) in which the **acyl residue** has a **high chemical potential**. It can therefore be transferred to other molecules in exergonic reactions. This fact plays an important role in lipid metabolism in particular (see pp. 162 ff.), as well as in two reactions of the tricarboxylic acid cycle (see p. 136).

As discussed on p. 16, the **group transfer potential** can be expressed quantitatively as the change in free enthalpy ($\Delta G$) during hydrolysis of the compound concerned. This is an arbitrary determination, but it provides important indications of the chemical energy stored in such a group. In the case of acetyl-CoA, the reaction to be considered is:

$$\text{Acetyl CoA} + H_2O \rightarrow \text{acetate} + \text{CoA}$$

In standard conditions and at pH 7, the change in the chemical potential G ($\Delta G^0$, see p. 18) in this reaction amounts to −32 kJ $mol^{-1}$ and it is therefore as high as the $\Delta G^0$ of ATP hydrolysis (see p. 18). In addition to the "energy-rich" **thioester bond**, acetyl-CoA also has seven other hydrolyzable bonds with different degrees of stability. These bonds, and the fragments that arise when they are hydrolyzed, will be discussed here in sequence.

(1) The reactive thiol group of coenzyme A is located in the part of the molecule that is derived from **cysteamine**. Cysteamine is a *biogenic amine* (see p. 62) formed by decarboxylation of the amino acid cysteine.

(2) The amino group of cysteamine is bound to the carboxy group of another biogenic amine via an **acid amide bond** (-CO-NH-). β-**Alanine** arises through decarboxylation of the amino acid aspartate, but it can also be formed by breakdown of pyrimidine bases (see p. 186).

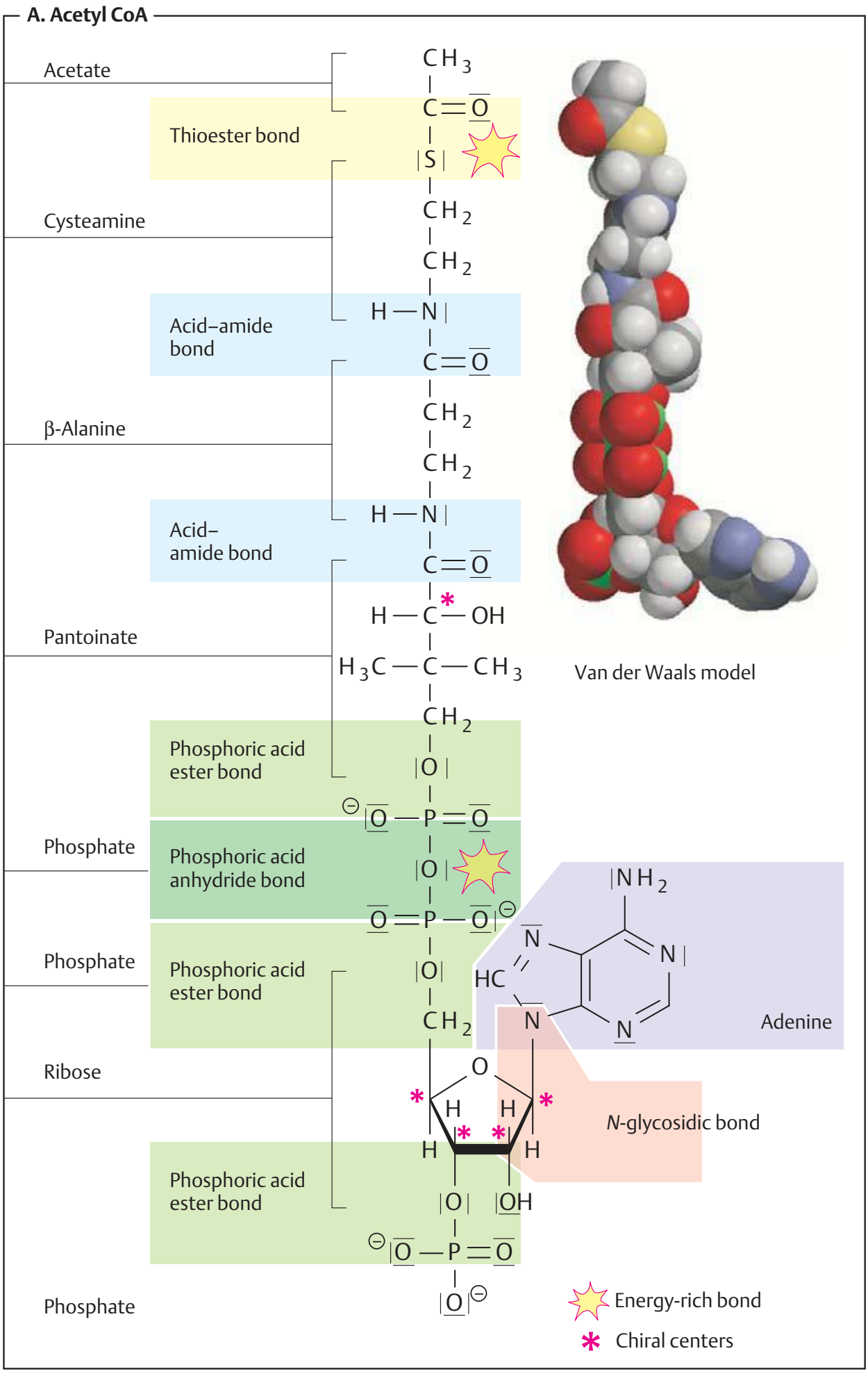
(3) Another **acid amide bond** (-CO-NH-) creates the compound for the next constituent, **pantoinate**. This compound contains a *chiral center* and can therefore appear in two enantiomeric forms (see p. 8). In natural coenzyme A, only one of the two forms is found, the (*R*)-pantoinate. Human metabolism is not capable of producing pantoinate itself, and it therefore has to take up a compound of β-alanine and pantoinate—**pantothenate** ("pantothenic acid")—in the form of a vitamin in food (see p. 366).

(4) The hydroxy group at C-4 of pantoinate is bound to a **phosphate** residue by an **ester bond**.

The section of the molecule discussed so far represents a functional unit. In the cell, it is produced from pantothenate. The molecule also occurs in a protein-bound form as **4′-phosphopantetheine** in the enzyme *fatty acid synthase* (see p. 168). In coenzyme A, however, it is bound to 3′,5′-adenosine diphosphate.

(5) When two phosphate residues bond, they do not form an ester, but an "energy-rich" **phosphoric acid anhydride bond**, as also occurs in other nucleoside phosphates. By contrast, (6) and (7) are ester bonds again.

(8) The base **adenine** is bound to C-1 of **ribose** by an **N-glycosidic** bond (see p. 36). In addition to C-2 to C-4, C-1 of ribose also represents a *chiral* center. The *β-configuration* is usually found in nucleotides.



## Chemical reactions

Chemical reactions are processes in which electrons or groups of atoms are taken up into molecules, exchanged between molecules, or shifted within molecules. Illustrated here are the most important types of reaction in organic chemistry, using simple examples. Electron shifts are indicated by red arrows.

### A. Redox reactions ◑

In redox reactions (see also p. 32), **electrons** are **transferred** from one molecule (the reducing agent) to another (the oxidizing agent). One or two protons are often also transferred in the process, but the decisive criterion for the presence of a redox reaction is the electron transfer. The reducing agent is oxidized during the reaction, and the oxidizing agent is reduced.

Fig. **A** shows the oxidation of an alcohol into an aldehyde (**1**) and the reduction of the aldehyde to alcohol (**2**). In the process, one *hydride ion* is transferred (two electrons and one proton; see p. 32), which moves to the oxidizing agent A in reaction **1**. The superfluous proton is bound by the catalytic effect of a base B. In the reduction of the aldehyde (**2**), A-H serves as the reducing agent and the acid H-B is involved as the catalyst.

### B. Acid–base reactions ◑

In contrast to redox reactions, only **proton transfer** takes place in acid–base reactions (see also p. 30). When an acid dissociates (**1**), water serves as a proton acceptor (i. e., as a base). Conversely, water has the function of an acid in the protonation of a carboxylate anion (**2**).

### C. Additions/eliminations ◑

A reaction in which atoms or molecules are taken up by a multiple bond is described as **addition**. The converse of addition—i. e., the removal of groups with the formation of a double bond, is termed **elimination**. When water is added to an alkene (**1a**), a proton is first transferred to the alkene. The unstable carbenium cation that occurs as an intermediate initially takes up water (not shown), before the separation of a proton produces alcohol (**1b**). The elimination of water from the alcohol (**2**, dehydration) is also catalyzed by an acid and passes via the same intermediate as the addition reaction.

### D. Nucleophilic substitutions ◑

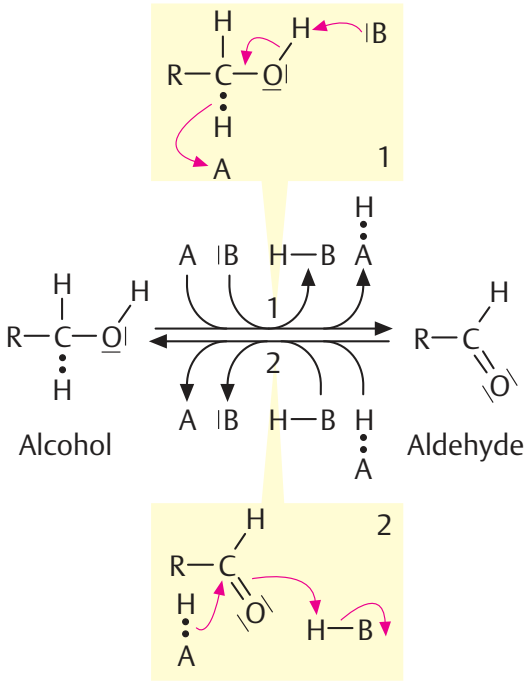
A reaction in which one functional group (see p. 10) is replaced by another is termed **substitution**. Depending on the process involved, a distinction is made between nucleophilic and electrophilic substitution reactions (see chemistry textbooks). Nucleophilic substitutions start with the addition of one molecule to another, followed by elimination of the so-called *leaving group*.

The hydrolysis of an ester to alcohol and acid (**1**) and the esterification of a carboxylic acid with an alcohol (**2**) are shown here as an example of the $S_N2$ mechanism. Both reactions are made easier by the marked polarity of the C=O double bond. In the form of ester hydrolysis shown here, a proton is removed from a water molecule by the catalytic effect of the base B. The resulting strongly nucleophilic $OH^-$ ion attacks the positively charged carbonyl C of the ester (**1a**), and an unstable $sp^3$-hybridized transition state is produced. From this, either water is eliminated (**2b**) and the ester re-forms, or the alcohol ROH is eliminated (**1b**) and the free acid results. In esterification (**2**), the same steps take place in reverse.

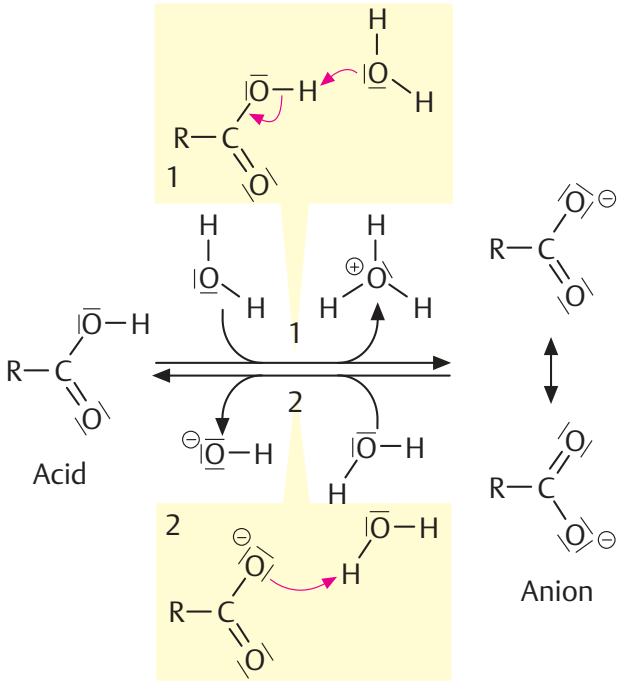
### Further information

In **rearrangements** (isomerizations, not shown), groups are shifted within one and the same molecule. Examples of this in biochemistry include the isomerization of sugar phosphates (see p. 36) and of methylmalonyl-CoA to succinyl CoA (see p. 166).

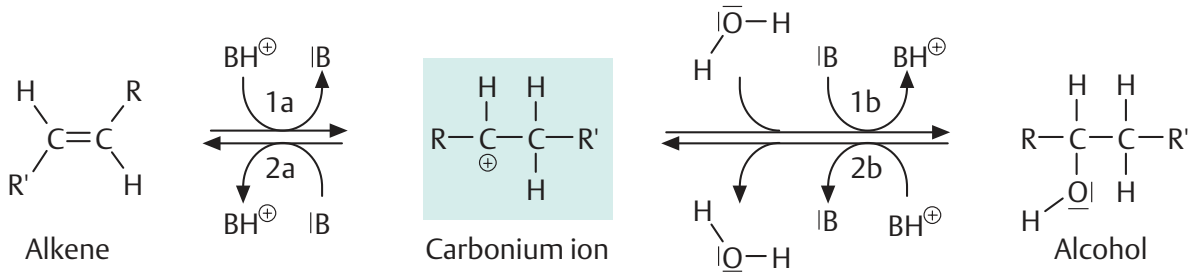
## A. Redox reactions



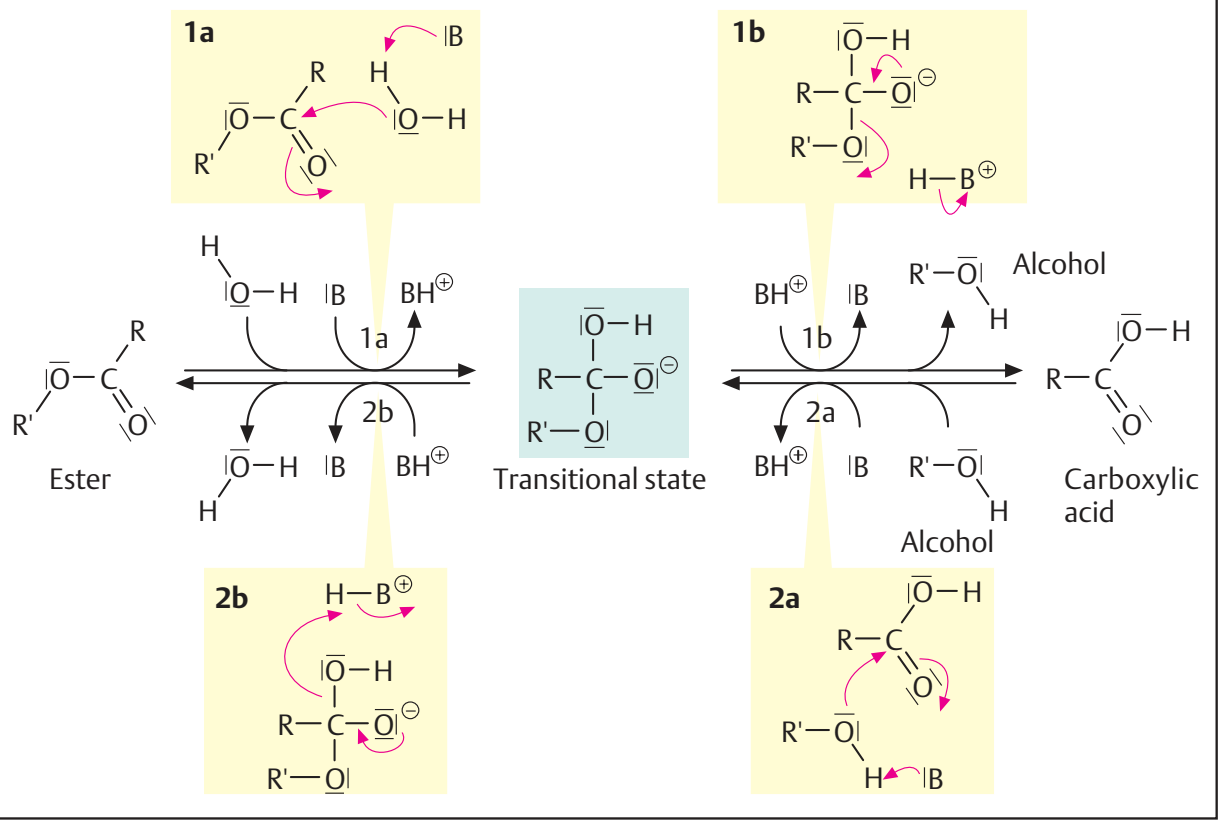

## B. Acid–base reactions




## C. Additions/eliminations




## D. Nucleophilic substitutions



## Energetics

To obtain a better understanding of the processes involved in energy storage and conversion in living cells, it may be useful first to recall the physical basis for these processes.

### A. Forms of work ●

There is essentially no difference between work and energy. Both are measured in **joule** (J = 1 N m). An outdated unit is the **calorie** (1 cal = 4.187 J). **Energy is defined as the ability of a system to perform work.** There are many different forms of energy—e.g., mechanical, chemical, and radiation energy.

A system is capable of performing work when matter is moving along a potential gradient. This abstract definition is best understood by an example involving mechanical work (**A1**). Due to the earth's gravitational pull, the mechanical potential energy of an object is the greater the further the object is away from the center of the earth. A **potential difference** ($\Delta P$) therefore exists between a higher location and a lower one. In a waterfall, the water spontaneously follows this potential gradient and, in doing so, is able to perform work—e.g., turning a mill.

Work and energy consist of two quantities: an **intensity** factor, which is a measure of the potential difference—i.e., the "driving force" of the process—(here it is the height difference) and a **capacity factor**, which is a measure of the quantity of the substance being transported (here it is the weight of the water). In the case of electrical work (**A2**), the intensity factor is the voltage—i.e., the electrical potential difference between the source of the electrical current and the "ground," while the capacity factor is the amount of charge that is flowing.

Chemical work and chemical energy are defined in an analogous way. The intensity factor here is the **chemical potential** of a molecule or combination of molecules. This is stated as **free enthalpy** *G* (also known as "Gibbs free energy"). When molecules spontaneously react with one another, the result is products at lower potential. The difference in the chemical potentials of the educts and products (the **change in free enthalpy**, $\Delta G$) is a measure of the "driving force" of the reaction. The capacity factor in chemical work is the amount of matter reacting (in mol). Although absolute values for free enthalpy G cannot be determined, $\Delta G$ can be calculated from the equilibrium constant of the reaction (see p. 18).

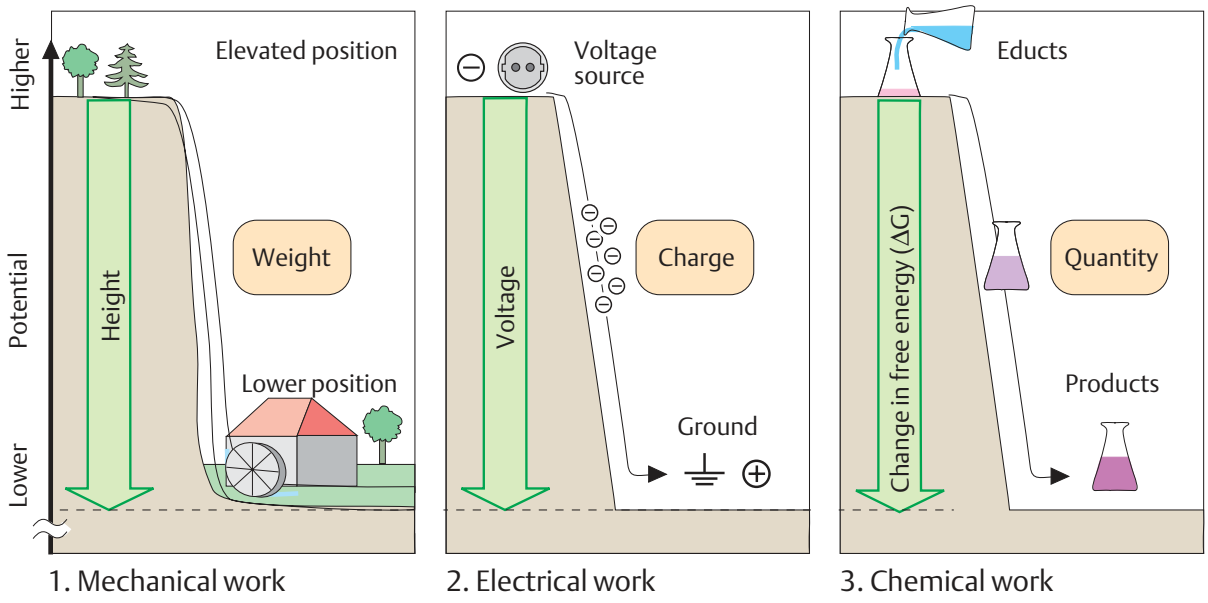
### B. Energetics and the course of processes ●

Everyday experience shows that water never flows uphill *spontaneously*. Whether a particular process can occur spontaneously or not depends on whether the potential difference between the final and the initial state, $\Delta P = P_2 - P_1$, is positive or negative. If $P_2$ is smaller than $P_1$, then $\Delta P$ will be negative, and the process will take place and perform work. Processes of this type are called **exergonic** (**B1**). If there is no potential difference, then the system is in **equilibrium** (**B2**). In the case of **endergonic** processes, $\Delta P$ is positive (**B3**). Processes of this type do *not* proceed spontaneously.

Forcing endergonic processes to take place requires the use of the principle of **energetic coupling**. This effect can be illustrated by a mechanical analogy (**B4**). When two masses $M_1$ and $M_2$ are connected by a rope, $M_1$ will move upward even though this part of the process is endergonic. The *sum* of the two potential differences ($\Delta P_{eff} = \Delta P_1 + \Delta P_2$) is the determining factor in coupled processes. When $\Delta P_{eff}$ is negative, the entire process can proceed.

Energetic coupling makes it possible to convert different forms of work and energy into one another. For example, in a flashlight, an exergonic chemical reaction provides an electrical voltage that can then be used for the endergonic generation of light energy. In the luminescent organs of various animals, it is a chemical reaction that produces the light. In the musculature (see p. 336), chemical energy is converted into mechanical work and heat energy. A form of storage for chemical energy that is used in all forms of life is **adenosine triphosphate** (ATP; see p. 122). Endergonic processes are usually driven by coupling to the strongly exergonic breakdown of ATP (see p. 122).

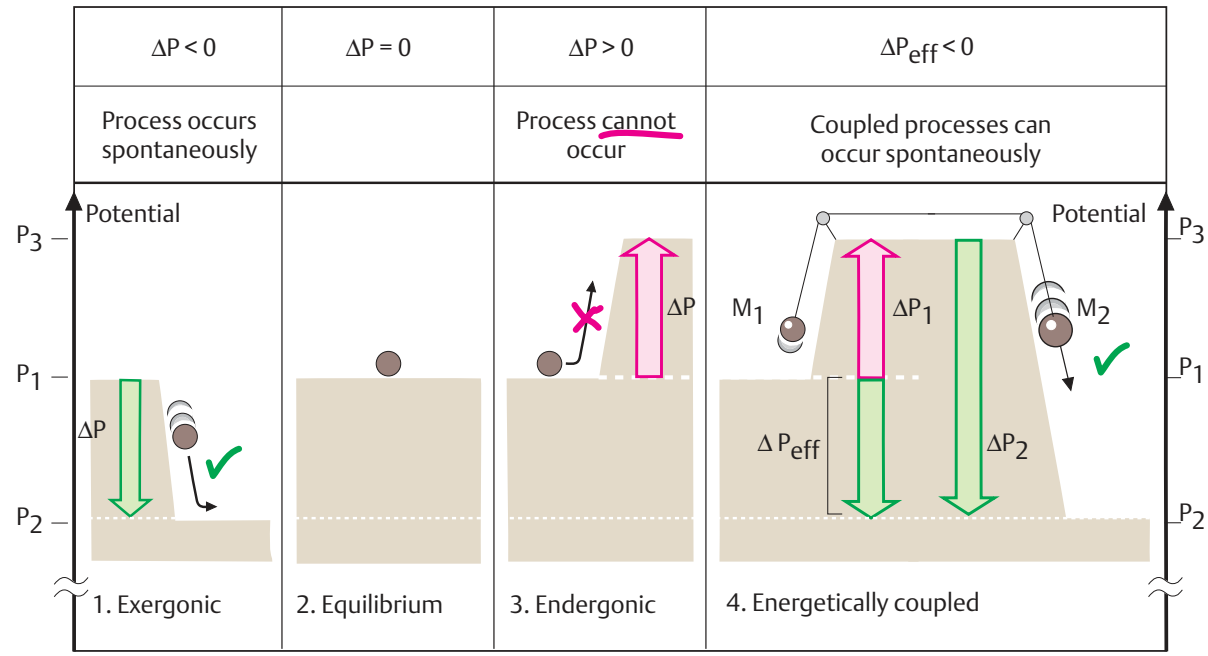
## A. Forms of work




J = Joule = N · m = 1 kg · $m^2$ · $s^{-2}$, 1 cal = 4.187 J

| Form of work | Intensity factor | Unit | Capacity factor | Unit | Work = ⇨ · ▭ | Unit |
|---|---|---|---|---|---|---|
| Mechanical | Height | m | Weight | $J \cdot m^{-1}$ | Height · Weight | J |
| Electrical | Voltage | $V = J \cdot C^{-1}$ | Charge | C | Voltage · Charge | J |
| Chemical | Free-enthalpy change ΔG | $J \cdot mol^{-1}$ | Quantity | mol | ΔG · Quantity | J |

## B. Energetics and the course of processes



## Equilibriums

### A. Group transfer reactions ◑

Every chemical reaction reaches after a time a **state of equilibrium** in which the forward and back reactions proceed at the same speed. The **law of mass action** describes the concentrations of the educts (A, B) and products (C, D) *in equilibrium.* The **equilibrium constant K** is directly related to $\Delta G^0$, the change in free enthalpy *G* involved in the reaction (see p. 16) under standard conditions ($\Delta G^0 = -$ R T ln K). For any given concentrations, the lower equation applies. At $\Delta G < 0$, the reaction proceeds spontaneously for as long as it takes for equilibrium to be reached (i. e., until $\Delta G = 0$). At $\Delta G > 0$, a *spontaneous* reaction is no longer possible (endergonic case; see p. 16). In biochemistry, $\Delta G$ is usually related to pH 7, and this is indicated by the "prime" symbol ($\Delta G^{0\prime}$ or $\Delta G'$).

As examples, we can look at two group transfer reactions (on the right). In ATP (see p. 122), the terminal phosphate residue is at a high chemical potential. Its transfer to water (reaction **a**, below) is therefore strongly **exergonic**. The equilibrium of the reaction ($\Delta G = 0$; see p. 122) is only reached when more than 99.9% of the originally available ATP has been hydrolyzed. ATP and similar compounds have a high **group transfer potential** for phosphate residues. Quantitatively, this is expressed as the **ΔG of hydrolysis** ($\Delta G^{0\prime} = -32$ kJ mol$^{-1}$; see p. 122).

In contrast, the **endergonic** transfer of ammonia ($NH_3$) to glutamate (Glu, reaction **b**, $\Delta G^{0\prime} = +14$ kJ mol$^{-1}$) reaches equilibrium so quickly that only minimal amounts of the product glutamine (Gln) can be formed in this way. The synthesis of glutamine from these preliminary stages is only possible through **energetic coupling** (see pp. 16, 124).

### B. Redox reactions ◑

The course of electron transfer reactions (redox reactions, see p. 14) also follows the law of mass action. For a single redox system (see p. 32), the Nernst equation applies (top). The **electron transfer potential** of a redox system (i. e., its tendency to give off or take up electrons) is given by its **redox potential E** (in standard conditions, $E^0$ or $E^{0\prime}$). The *lower* the redox potential of a system is, the *higher* the chemical potential of the transferred electrons. To describe reactions between two redox systems, $\Delta E$—the difference between the two systems' redox potentials—is usually used instead of $\Delta G$. $\Delta G$ and $\Delta E$ have a simple relationship, but opposite signs (below). A redox reaction proceeds spontaneously when $\Delta E > 0$, i. e. $\Delta G < 0$.

The right side of the illustration shows the way in which the redox potential E is dependent on the composition (the proportion of the reduced form as a %) in two biochemically important redox systems (pyruvate/lactate and $NAD^+/NADH+H^+$; see pp. 98, 104). In the standard state (both systems reduced to 50%), electron transfer from lactate to $NAD^+$ is *not* possible, because $\Delta E$ is negative ($\Delta E = -0.13$ V, red arrow). By contrast, transfer can proceed successfully if the pyruvate/lactate system is reduced to 98% and $NAD^+$/NADH is 98% oxidized (green arrow, $\Delta E = +0.08$ V).

### C. Acid–base reactions ◑

Pairs of *conjugated* acids and bases are always involved in proton exchange reactions (see p. 30). The dissociation state of an acid–base pair depends on the $H^+$ concentration. Usually, it is not this concentration itself that is expressed, but its negative decadic logarithm, the **pH value**. The connection between the pH value and the dissociation state is described by the *Henderson–Hasselbalch equation* (below). As a measure of the **proton transfer potential** of an acid–base pair, its **$pK_a$ value** is used—the negative logarithm of the acid constant $K_a$ (where "a" stands for acid).

The *stronger* an acid is, the *lower* its $pK_a$ value. The acid of the pair with the lower $pK_a$ value (the stronger acid—in this case acetic acid, $CH_3COOH$) can protonate (green arrow) the base of the pair with the higher $pK_a$ (in this case $NH_3$), while ammonium acetate ($NH_4^+$ and $CH_3COO^-$) only forms very little $CH_3COOH$ and $NH_3$.

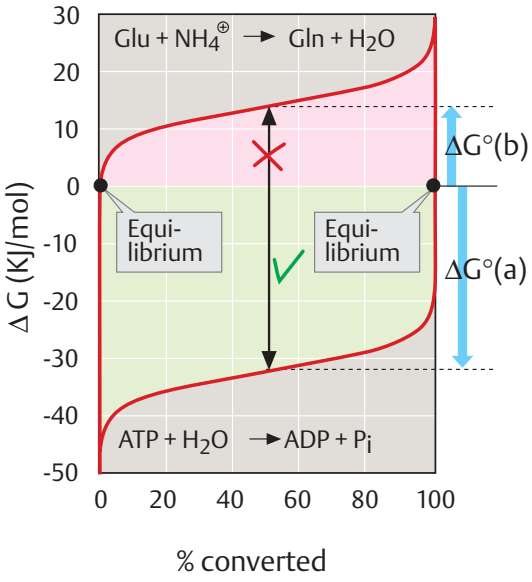
## A. Group transfer reactions

Reaction: $A + B \rightleftharpoons C + D$

Law of mass action: $K = \frac{[C] \cdot [D]}{[A] \cdot [B]}$ (Only applies in chemical equilibrium; Equilibrium constant)

Relationship between $\Delta G^0$ and K: $\Delta G^\circ = -R \cdot T \cdot \ln K$, $R = 8.314\ J \cdot mol^{-1} \cdot K^{-1}$

In any conditions: $\Delta G = \Delta G^\circ + R \cdot T \cdot \ln \frac{[C] \cdot [D]}{[A] \cdot [B]}$ (Measure of group transfer potential)




## B. Redox reactions

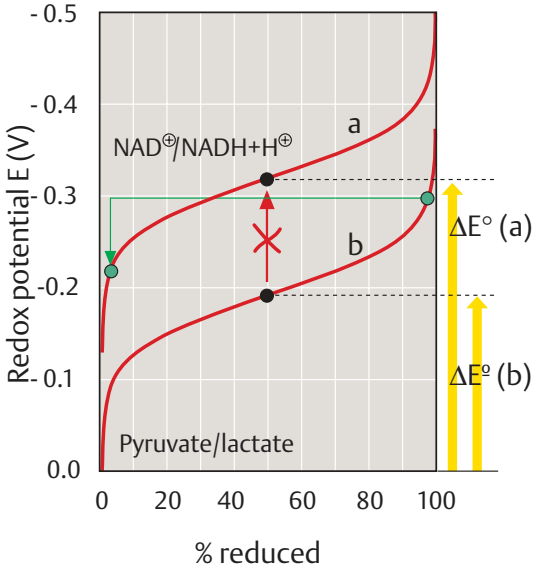
$A_{red} \rightleftharpoons A_{ox}$

For a redox system: $E = E^\circ + \frac{R \cdot T}{n \cdot F} \cdot \ln \frac{[A_{ox}]}{[A_{red}]}$ (Measure of electron transfer potential)

For any redox reaction: $\Delta E = \Delta E^\circ + \frac{R \cdot T}{n \cdot F} \cdot \ln \frac{[B_{ox}] \cdot [A_{red}]}{[B_{red}] \cdot [A_{ox}]}$

Definition and sizes: $\Delta E = E_{Acceptor} - E_{Donor}$, $\Delta G = -n \cdot F \cdot \Delta E$

n = No. of electrons transferred
F = Faraday constant



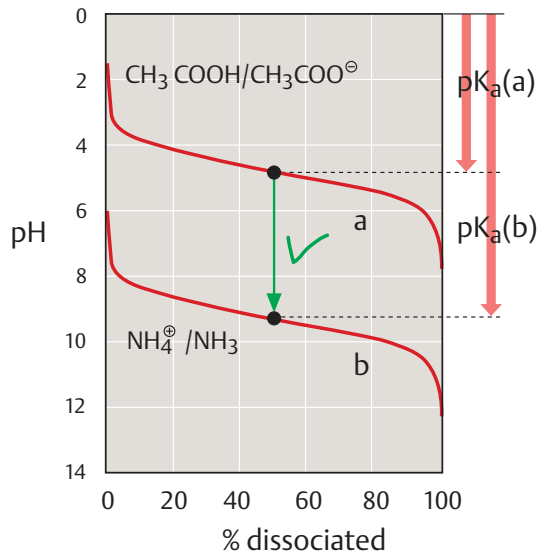

## C. Acid–base reactions

Standard reaction: $HA + H_2O \rightleftharpoons A^\ominus + H_3O^\oplus$

Law of mass action: $K = \frac{[A^\ominus] \cdot [H_3O^\oplus]}{[HA] \cdot [H_2O]}$

Simplified: $K_a = \frac{[A^\ominus] \cdot [H^\oplus]}{[HA]}$

Henderson–Hasselbalch equation: $pH = pK_a + \log \frac{[A^\ominus]}{[HA]}$ (Measure of proton transfer potential)



## Enthalpy and entropy

The change in the free enthalpy of a chemical reaction (i.e., its $\Delta G$) depends on a number of factors—e.g., the concentrations of the reactants and the temperature (see p. 18). Two further factors associated with molecular changes occurring during the reaction are discussed here.

### A. Heat of reaction and calorimetry ◑

All chemical reactions involve heat exchange. Reactions that release heat are called **exothermic**, and those that consume heat are called **endothermic**. Heat exchange is measured as the enthalpy change $\Delta H$ (the heat of reaction). This corresponds to the heat exchange at constant pressure. In exothermic reactions, the system *loses* heat, and $\Delta H$ is negative. When the reaction is endothermic, the system gains heat, and $\Delta H$ becomes positive.

In many reactions, $\Delta H$ and $\Delta G$ are similar in magnitude (see **B1**, for example). This fact is used to estimate the caloric content of foods. In living organisms, nutrients are usually oxidized by oxygen to $CO_2$ and $H_2O$ (see p. 112). The maximum amount of chemical work supplied by a particular foodstuff (i.e., the $\Delta G$ for the oxidation of the utilizable constituents) can be estimated by burning a weighed amount in a **calorimeter** in an oxygen atmosphere. The heat of the reaction increases the water temperature in the calorimeter. The reaction heat can then be calculated from the temperature difference $\Delta T$.

### B. Enthalpy and entropy ◑

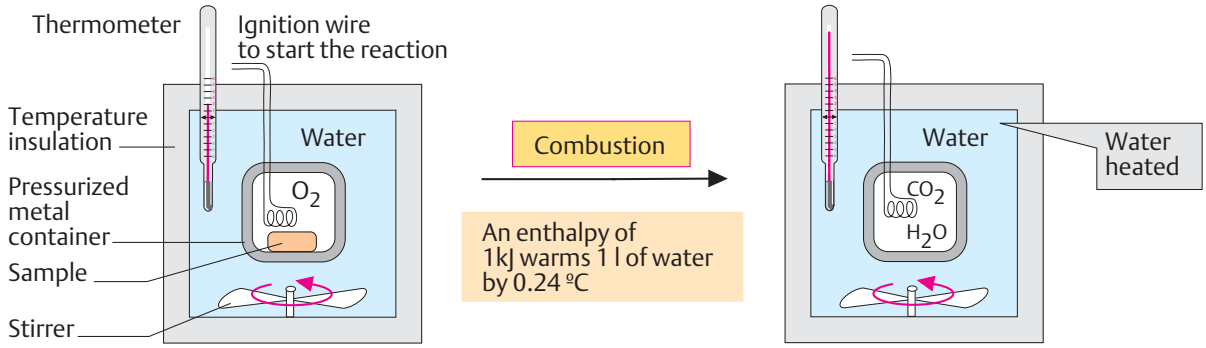
The reaction enthalpy $\Delta H$ and the change in free enthalpy $\Delta G$ are not always of the same magnitude. There are even reactions that occur spontaneously ($\Delta G < 0$) even though they are endothermic ($\Delta H > 0$). The reason for this is that changes in the degree of order of the system also strongly affect the progress of a reaction. This change is measured as the **entropy change ($\Delta S$)**.

**Entropy** is a physical value that describes the **degree of order of a system**. The *lower* the degree of order, the larger the entropy. Thus, when a process leads to increase in disorder—and everyday experience shows that this is the normal state of affairs—$\Delta S$ is positive for this process. An increase in the order in a system ($\Delta S < 0$) always requires an input of energy. Both of these statements are consequences of an important natural law, the Second Law of Thermodynamics. The connection between changes in enthalpy and entropy is described quantitatively by the **Gibbs–Helmholtz equation** ($\Delta G = \Delta H - T\ \Delta S$). The following examples will help explain these relationships.

In the *knall-gas* **(oxyhydrogen) reaction** (**1**), gaseous oxygen and gaseous hydrogen react to form liquid water. Like many redox reactions, this reaction is strongly exothermic (i.e., $\Delta H < 0$). However, during the reaction, the degree of order increases. The total number of molecules is reduced by one-third, and a more highly ordered liquid is formed from freely moving gas molecules. As a result of the increase in the degree of order ($\Delta S < 0$), the term $-T\ \Delta S$ becomes positive. However, this is more than compensated for by the decrease in enthalpy, and the reaction is still strongly exergonic ($\Delta G < 0$).

The **dissolution of salt in water** (**2**) is endothermic ($\Delta H > 0$)—i.e., the liquid cools. Nevertheless, the process still occurs spontaneously, since the degree of order in the system *decreases*. The $Na^+$ and $Cl^-$ ions are initially rigidly fixed in a crystal lattice. In solution, they move about independently and in random directions through the fluid. The decrease in order ($\Delta S > 0$) leads to a negative $-T\ \Delta S$ term, which compensates for the positive $\Delta H$ term and results in a negative $\Delta G$ term overall. Processes of this type are described as being **entropy-driven**. The folding of proteins (see p. 74) and the formation of ordered lipid structures in water (see p. 28) are also mainly entropy-driven.

## A. Heat of reaction and calorimetry



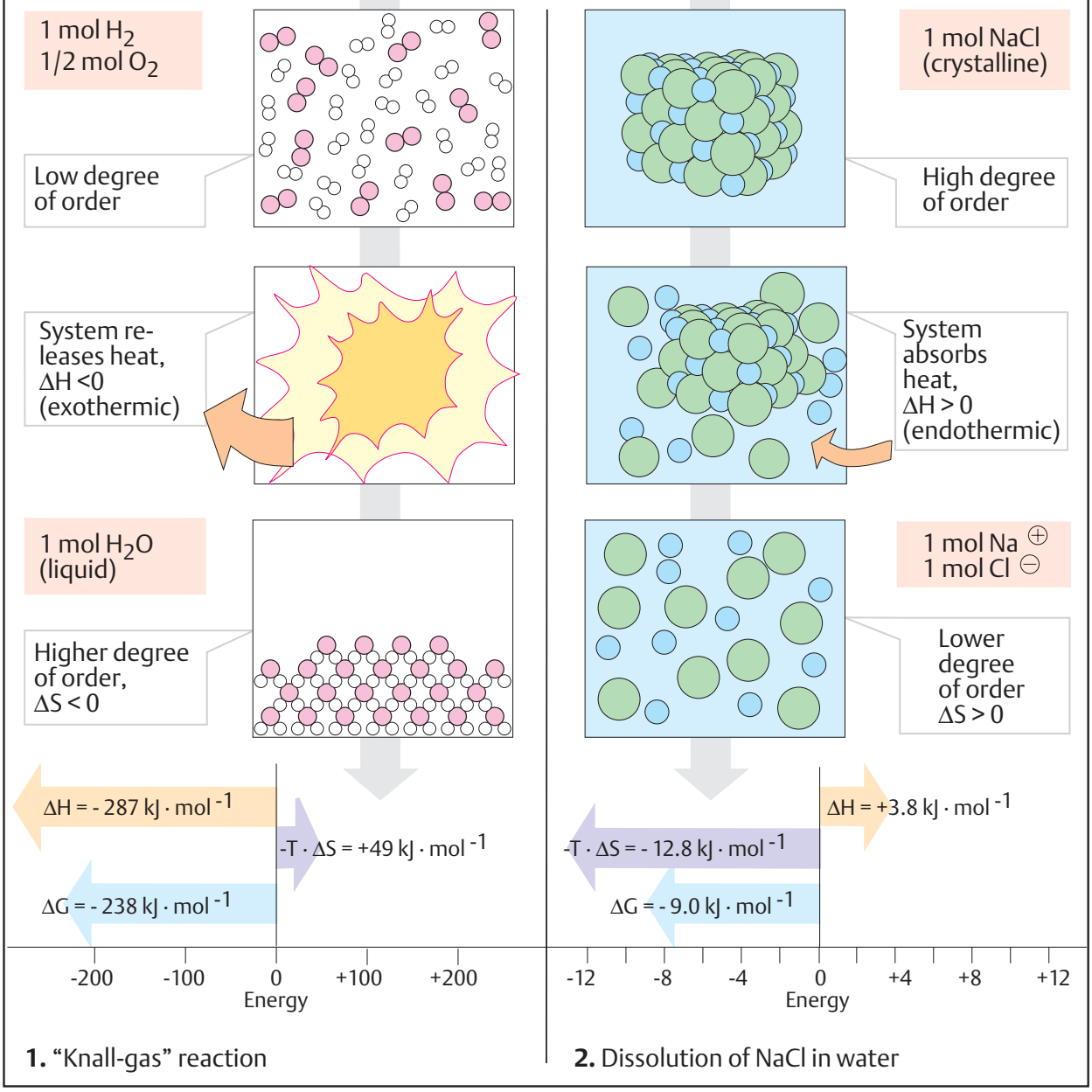

## B. Enthalpy and entropy

$\Delta G = \Delta H - T \cdot \Delta S$

Gibbs-Helmholtz equation

ΔH: change of enthalpy, heat exchange

ΔS: change of entropy, i.e. degree of order



## Reaction kinetics

The change in free enthalpy $\Delta G$ in a reaction indicates whether or not the reaction can take place spontaneously in given conditions and how much work it can perform (see p. 18). However, it does not tell us anything about the *rate* of the reaction—i. e., its **kinetics**.

### A. Activation energy ◑

Most organic chemical reactions (with the exception of acid–base reactions) proceed only very slowly, regardless of the value of $\Delta G$. The reason for the slow reaction rate is that the molecules that react—the educts—have to have a certain minimum energy before they can enter the reaction. This is best understood with the help of an energy diagram (**1**) of the simplest possible reaction $A \rightarrow B$. The educt A and the product B are each at a specific **chemical potential** ($G_e$ and $G_p$, respectively). The change in the free enthalpy of the reaction, $\Delta G$, corresponds to the difference between these two potentials. To be converted into B, A first has to overcome a potential energy barrier, the peak of which, $G_a$, lies well above $G_e$. The potential difference $G_a - G_e$ is the **activation energy $E_a$** of the reaction (in kJ $mol^{-1}$).

The fact that A can be converted into B at all is because the potential $G_e$ only represents the average potential of all the molecules. Individual molecules may occasionally reach much higher potentials—e. g., due to collisions with other molecules. When the increase in energy thus gained is greater than $E_a$, these molecules can overcome the barrier and be converted into B. The energy distribution for a group of molecules of this type, as calculated from a simple model, is shown in (**2**) and (**3**). $\Delta n/n$ is the fraction of molecules that have reached or exceeded energy E (in kJ per mol). At 27 °C, for example, approximately 10% of the molecules have energies > 6 kJ $mol^{-1}$. The typical activation energies of chemical reactions are much higher. The course of the energy function at energies of around 50 kJ $mol^{-1}$ is shown in (**3**). Statistically, at 27 °C only two out of $10^9$ molecules reach this energy. At 37 °C, the figure is already four. This is the basis for the long-familiar "$Q_{10}$ law"—a rule of thumb that states that the speed of biological processes approximately doubles with an increase in temperature of 10 °C.

### B. Reaction rate ◑

The velocity *v* of a chemical reaction is determined experimentally by observing the change in the concentration of an educt or product over time. In the example shown (again a reaction of the $A \rightarrow B$ type), 3 mmol of the educt A is converted per second and 3 mmol of the product B is formed per second in one liter of the solution. This corresponds to a rate of

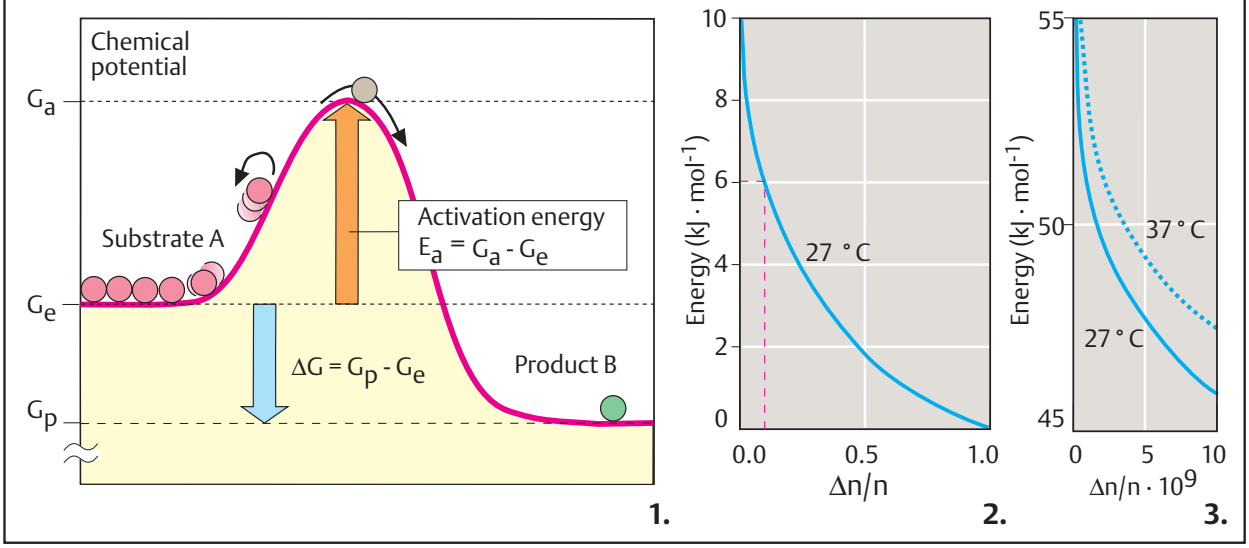
$$v = 3 \text{ mM } s^{-1} = 3 \text{ } 10^{-3} \text{ mol } L^{-1} \text{ } s^{-1}$$

### C. Reaction order ◑

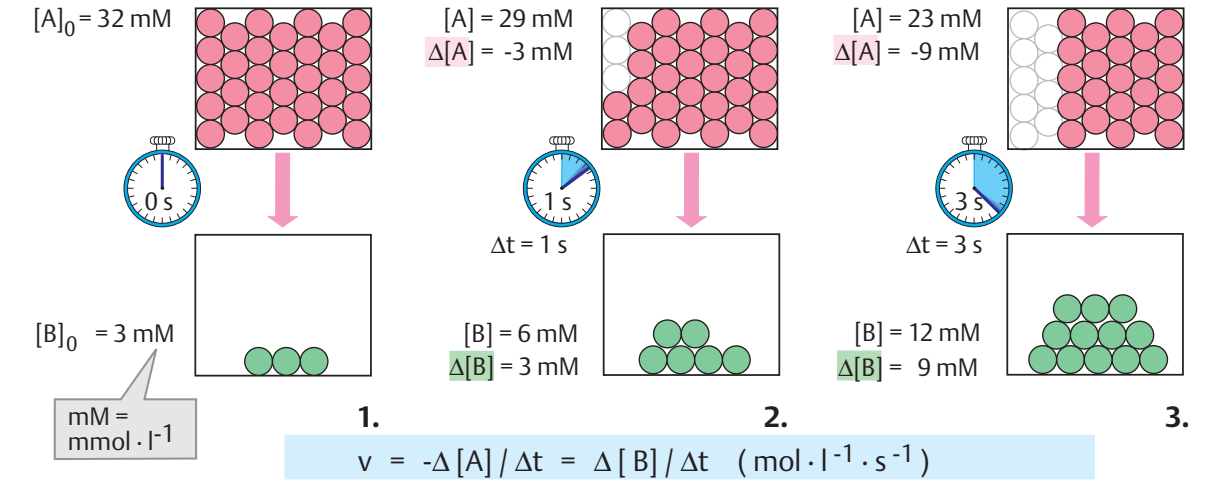
Reaction rates are influenced not only by the activation energy and the temperature, but also by the concentrations of the reactants. When there is only one educt, A (**1**), *v* is proportional to the concentration [A] of this substance, and a **first-order reaction** is involved. When *two* educts, A and B, react with one another (**2**), it is a **second order reaction** (shown on the right). In this case, the rate *v* is proportional to the *product* of the educt concentrations (12 $mM^2$ at the top, 24 $mM^2$ in the middle, and 36 $mM^2$ at the bottom). The proportionality factors k and k′ are the **rate constants** of the reaction. They are *not* dependent on the reaction concentrations, but depend on the external conditions for the reaction, such as temperature.

In **B**, only the kinetics of simple irreversible reactions is shown. More complicated cases, such as reaction with three or more reversible steps, can usually be broken down into first-order or second-order partial reactions and described using the corresponding equations (for an example, see the Michaelis–Menten reaction, p. 92).

## A. Activation energy

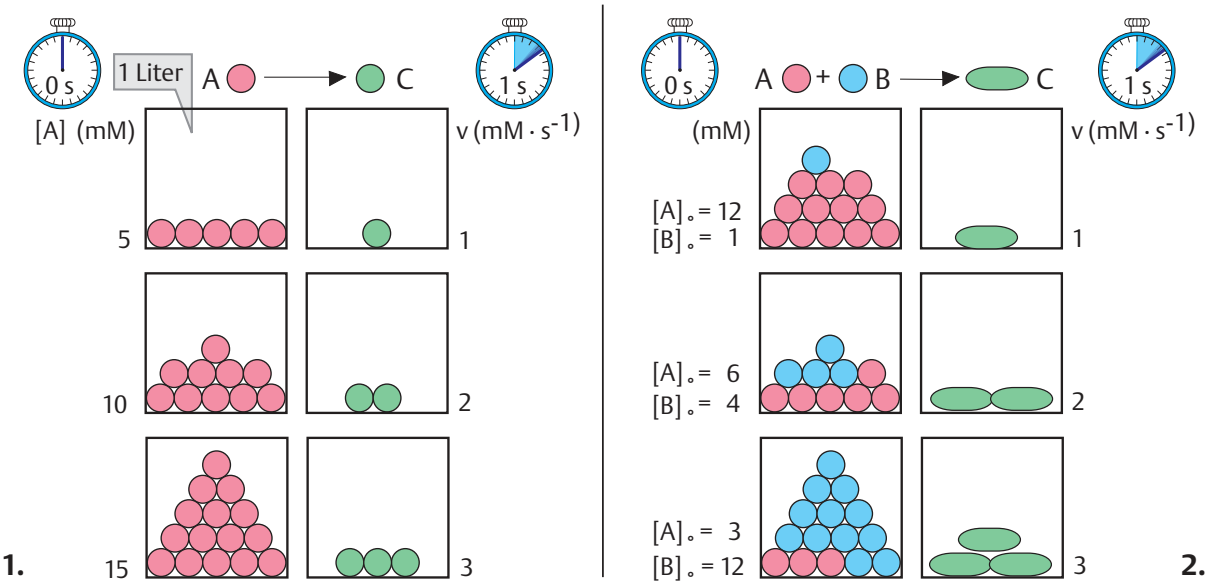



## B. Reaction rate




$$v = -\Delta[A]/\Delta t = \Delta[B]/\Delta t \quad (\text{mol} \cdot \text{l}^{-1} \cdot \text{s}^{-1})$$

## C. Reaction order




$v = k \cdot [A]$ — k, k' : Rate constants — $v = k' \cdot [A] \cdot [B]$

First-order reaction: $k = 1/5\ s^{-1}$

Second-order reaction: $k' = 1/12\ l \cdot mmol^{-1} \cdot s^{-1}$

## Catalysis

Catalysts are substances that accelerate chemical reactions without themselves being consumed in the process. Since catalysts emerge from the catalyzed reaction without being changed, even small amounts are usually suf cient to cause a powerful acceleration of the reaction. In the cell, **enzymes** (see p. 88) generally serve as catalysts. A few chemical changes are catalyzed by special RNA molecules, known as *ribozymes* (see p. 246).

### A. Catalysis: principle ●

The reason for the slow rates of most reactions involving organic substances is the high **activation energy** (see p. 22) that the reacting molecules have to reach before they can react. In aqueous solution, a large proportion of the activation energy is required to remove the hydration shells surrounding the educts. During the course of a reaction, resonance-stabilized structures (see p. 4) are often temporarily suspended; this also requires energy. The highest point on the reaction coordinates corresponds to an energetically unfavorable **transition state** of this type (**1**).

A catalyst creates a new pathway for the reaction (**2**). When all of the transition states arising have a lower activation energy than that of the uncatalyzed reaction, the reaction will proceed more rapidly along the alternative pathway, even when the number of intermediates is greater. Since the starting points and end points are the same in both routes, the change in the enthalpy $\Delta G$ of the reaction is not influenced by the catalyst. Catalysts—including enzymes—are in principle *not* capable of altering the equilibrium state of the catalyzed reaction.

The often-heard statement that "a catalyst reduces the activation energy of a reaction" is not strictly correct, since a *completely different* reaction takes place in the presence of a catalyst than in uncatalyzed conditions. However, its activation energy is lower than in the uncatalyzed reaction.

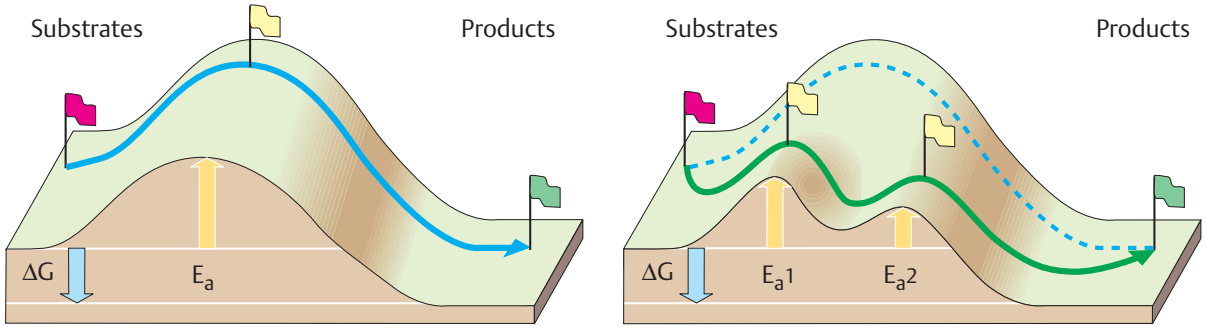
### B. Catalysis of $H_2O_2$ – breakdown by iodide ○

As a simple example of a catalyzed reaction, we can look at the disproportionation of hydrogen peroxide ($H_2O_2$) into oxygen and water. In the uncatalyzed reaction (at the top), an $H_2O_2$ molecule initially decays into $H_2O$ and atomic oxygen (O), which then reacts with a second $H_2O_2$ molecule to form water and molecular oxygen ($O_2$). The activation energy $E_a$ required for this reaction is relatively high, at 75 kJ mol$^{-1}$. In the presence of **iodide** ($I^-$) as a catalyst, the reaction takes a different course (bottom). The intermediate arising in this case is hypoiodide ($OI^-$), which also forms $H_2O$ and $O_2$ with another $H_2O_2$ molecule. In this step, the $I^-$ ion is released and can once again take part in the reaction. The lower activation energy of the reaction catalyzed by iodide ($E_a$ = 56 kJ mol$^{-1}$) causes acceleration of the reaction by a factor of 2000, as the reaction rate depends exponentially on $E_a$ ($v \sim e^{-Ea/R\,T}$).

Free metal ions such as iron (Fe) and platinum (Pt) are also effective catalysts for the breakdown of $H_2O_2$. **Catalase** (see p. 284), an enzyme that protects cells against the toxic effects of hydrogen peroxide (see p. 284), is much more catalytically effective still. In the enzyme-catalyzed disproportionation, $H_2O_2$ is bound to the enzyme's heme group, where it is quickly converted to atomic oxygen and water, supported by amino acid residues of the enzyme protein. The oxygen atom is temporarily bound to the central iron atom of the heme group, and then transferred from there to the second $H_2O_2$ molecule. The activation energy of the enzyme-catalyzed reaction is only 23 kJ mol$^{-1}$, which in comparison with the uncatalyzed reaction leads to acceleration by a factor of 1.3 $10^9$.

Catalase is one of the most ef cient enzymes there are. A single molecule can convert up to $10^8$ (a hundred million) $H_2O_2$ molecules per second.

## A. Catalysis: principle

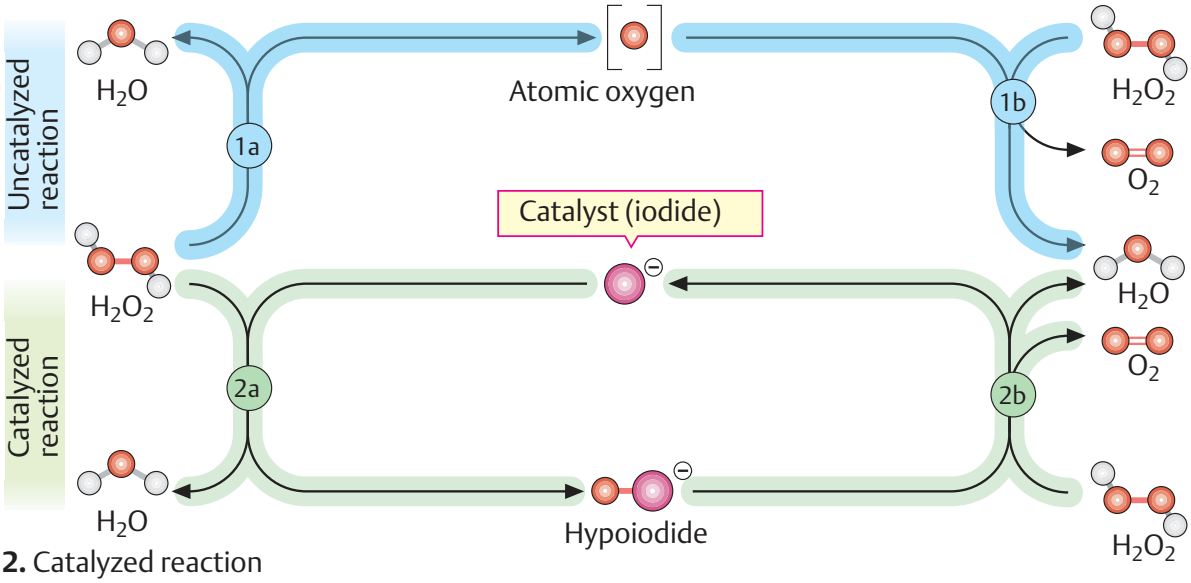



**1.** Energy profile without catalyst

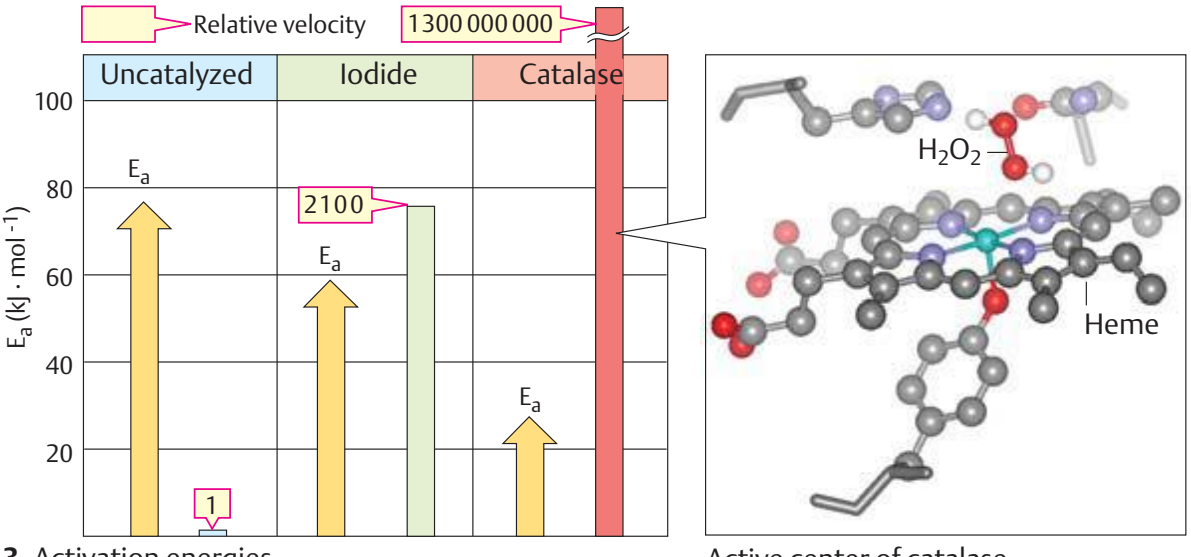
**2.** Energy profile with catalyst

## B. Catalysis of $H_2O_2$ – breakdown by iodide


**1.** Breakdown of hydrogen peroxide




**2.** Catalyzed reaction




**3.** Activation energies

Active center of catalase

## Water as a solvent

Life as we know it evolved in water and is still absolutely dependent on it. The properties of water are therefore of fundamental importance to all living things.

### A. Water and methane ◑

The special properties of **water ($H_2O$)** become apparent when it is compared with **methane ($CH_4$)**. The two molecules have a similar mass and size. Nevertheless, the boiling point of water is more than 250 °C above that of methane. At temperatures on the earth's surface, water is liquid, whereas methane is gaseous. The high boiling point of water results from its high vaporization enthalpy, which in turn is due to the fact that the density of the electrons within the molecule is unevenly distributed. Two corners of the tetrahedrally-shaped water molecule are occupied by unshared electrons (green), and the other two by hydrogen atoms. As a result, the H–O–H bond has an angled shape. In addition, the O–H bonds are polarized due to the high electronegativity of oxygen (see p. 6). One side of the molecule carries a partial charge (δ) of about –0.6 units, whereas the other is correspondingly positively charged. The spatial separation of the positive and negative charges gives the molecule the properties of an **electrical dipole**. Water molecules are therefore attracted to one another like tiny magnets, and are also connected by hydrogen bonds (**B**) (see p. 6). When liquid water vaporizes, a large amount of energy has to be expended to disrupt these interactions. By contrast, methane molecules are not dipolar, and therefore interact with one another only weakly. This is why liquid methane vaporizes at very low temperatures.

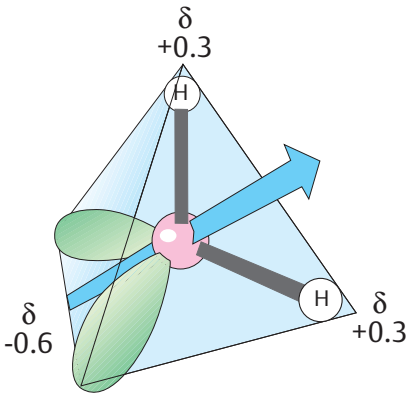
### B. Structure of water and ice ◑

The dipolar nature of water molecules favors the formation of **hydrogen bonds** (see p. 6). Each molecule can act either as a donor or an acceptor of H bonds, and many molecules in liquid water are therefore connected by H bonds (**1**). The bonds are in a state of constant fluctuation. Tetrahedral networks of molecules, known as water "clusters," often arise. As the temperature decreases, the proportion of water clusters increases until the water begins to crystallize. Under normal atmospheric pressure, this occurs at 0 °C. In **ice**, most of the water molecules are fixed in a **hexagonal lattice** (**3**). Since the distance between the individual molecules in the frozen state is on average greater than in the liquid state, the density of ice is lower than that of liquid water. This fact is of immense biological importance—it means, for example, that in winter, ice forms on the surface of open stretches of water first, and the water rarely freezes to the bottom.

### C. Hydration ◑

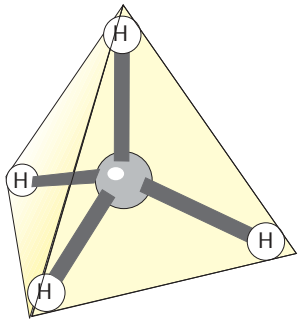
In contrast to most other liquids, water is an excellent **solvent for ions**. In the electrical field of cations and anions, the dipolar water molecules arrange themselves in a regular fashion corresponding to the charge of the ion. They form **hydration shells** and shield the central ion from oppositely charged ions. Metal ions are therefore often present as hexahydrates ($[Me(H_2O)_6^{2+}]$, on the right). In the inner hydration sphere of this type of ion, the water molecules are practically immobilized and follow the central ion. Water has a high dielectric constant of 78—i. e., the electrostatic attraction force between ions is reduced to 1/78 by the solvent. Electrically charged groups in organic molecules (e. g., carboxylate, phosphate, and ammonium groups) are also well hydrated and contribute to water solubility. Neutral molecules with several hydroxy groups, such as glycerol (on the left) or sugars, are also easily soluble, because they can form H bonds with water molecules. The higher the proportion of polar functional groups there is in a molecule, the more water-soluble (**hydrophilic**) it is. By contrast, molecules that consist exclusively or mainly of hydrocarbons are poorly soluble or insoluble in water. These compounds are called **hydrophobic** (see p. 28).

## A. Water and methane



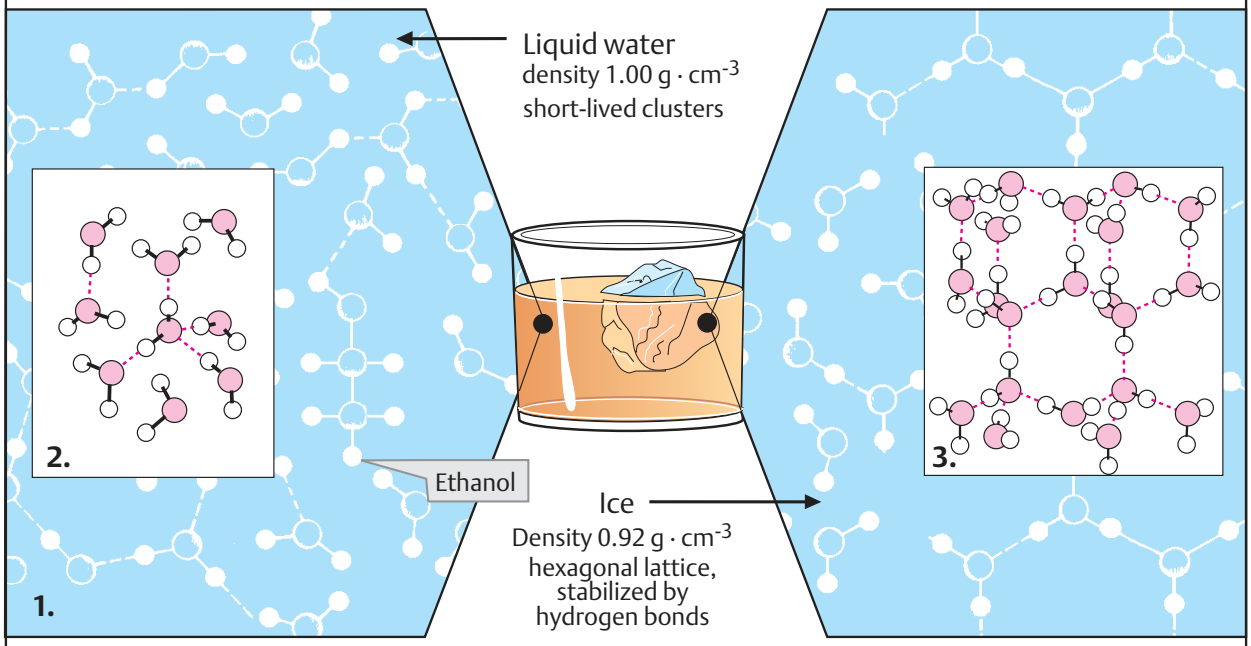

Water ($H_2O$)

| $H_2O$ | | $CH_4$ |
|---|---|---|
| 18 Da | Molecular mass | 16 Da |
| +100 °C | Boiling point | -162 °C |
| 41 | Heat of vaporization ($kJ \cdot mol^{-1}$) | 8 |
| 6.2 | Dipole moment ($10^{-30}$ C · m) | 0 |

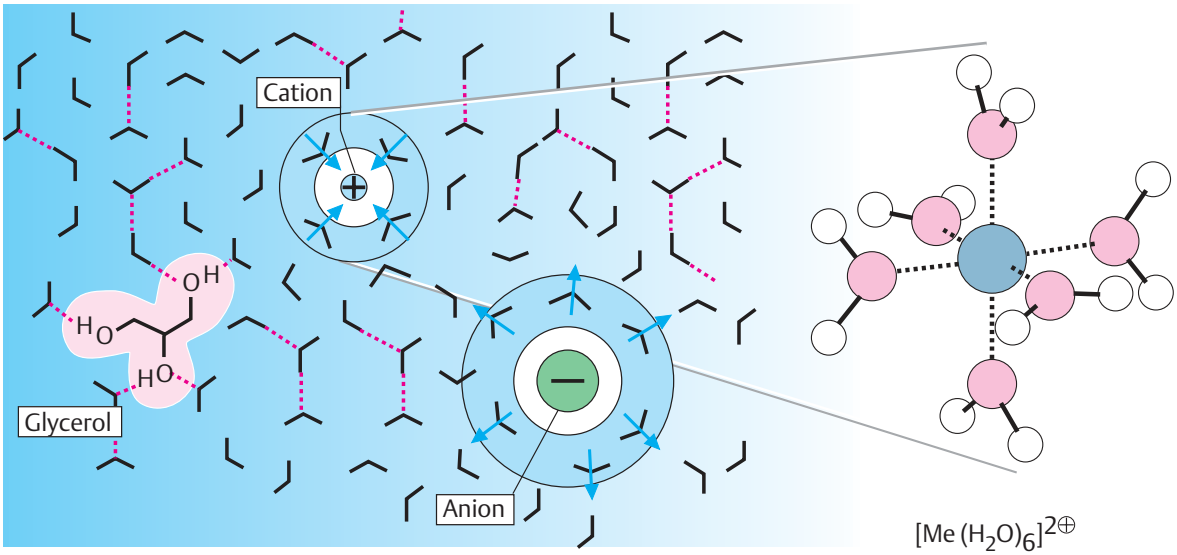



Methane ($CH_4$)

## B. Structure of water and ice




## C. Hydration



## Hydrophobic interactions

Water is an excellent solvent for ions and for substances that contain polarized bonds (see p. 20). Substances of this type are referred to as **polar** or **hydrophilic** ("water-loving"). In contrast, substances that consist mainly of hydrocarbon structures dissolve only poorly in water. Such substances are said to be **apolar** or **hydrophobic**.

### A. Solubility of methane ○

To understand the reasons for the poor water solubility of hydrocarbons, it is useful first to examine the energetics (see p. 16) of the processes involved. In (**1**), the individual terms of the Gibbs–Helmholtz equation (see p. 20) for the simplest compound of this type, **methane**, are shown (see p. 4). As can be seen, the transition from gaseous methane to water is actually exothermic ($\Delta H^0 < 0$). Nevertheless, the change in the free enthalpy $\Delta G^0$ is positive (the process is endergonic), because the entropy term $T\ \Delta S^0$ has a strongly positive value. The entropy change in the process ($\Delta S^0$) is evidently negative—i. e., a solution of methane in water has a *higher* degree of order than either water or gaseous methane. One reason for this is that the methane molecules are less mobile when surrounded by water. More importantly, however, the water around the apolar molecules forms cage-like **"clathrate" structures**, which—as in ice—are stabilized by H bonds. This strongly increases the degree of order in the water—and the more so the larger the area of surface contact between the water and the apolar phase.

### B. The "oil drop effect" ◑

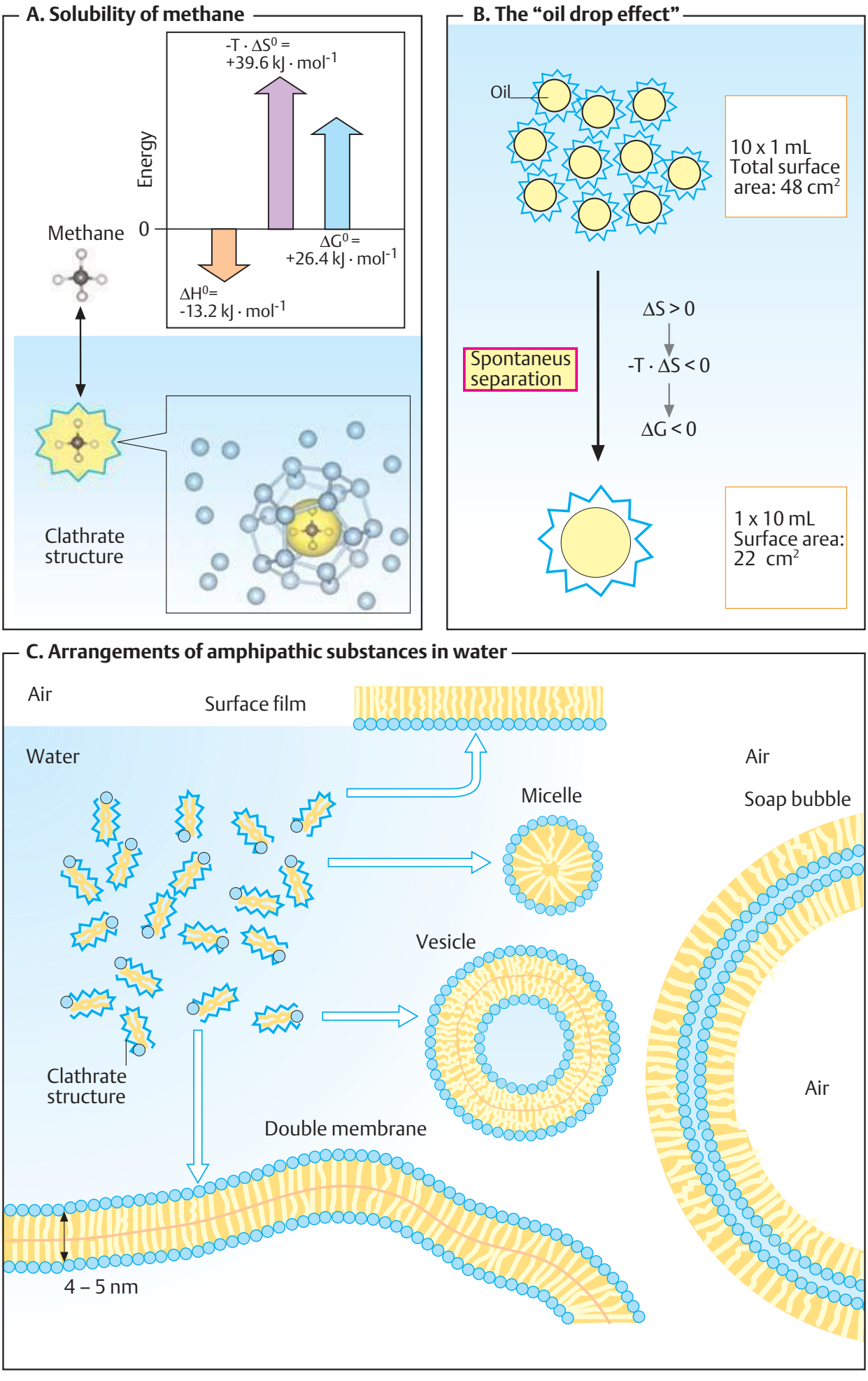
The spontaneous separation of oil and water, a familiar observation in everyday life, is due to the energetically unfavorable formation of clathrate structures. When a mixture of water and oil is firmly shaken, lots of tiny oil drops form to begin with, but these quickly coalesce spontaneously to form larger drops—the two phases separate. A larger drop has a smaller surface area than several small drops with the same volume. Separation therefore reduces the area of surface contact between the water and the oil, and consequently also the extent of clathrate formation. The $\Delta S$ for this process is therefore positive (the *dis*order in the water increases), and the negative term $-T\ \Delta S$ makes the separation process exergonic ($\Delta G < 0$), so that it proceeds spontaneously.

### C. Arrangements of amphipathic substances in water ◑

Molecules that contain both polar *and* apolar groups are called **amphipathic** or amphiphilic. This group includes soaps (see p. 48), phospholipids (see p. 50), and bile acids (see p. 56).

As a result of the "oil drop effect" amphipathic substances in water tend to arrange themselves in such a way as to minimize the area of surface contact between the apolar regions of the molecule and water. On water surfaces, they usually form single-layer **films** (top) in which the polar "head groups" face toward the water. **Soap bubbles** (right) consist of double films, with a thin layer of water enclosed between them. In water, depending on their concentration, amphipathic compounds form **micelles**—i. e., spherical aggregates with their head groups facing toward the outside, or extended bilayered **double membranes**. Most biological membranes are assembled according to this principle (see p. 214). Closed hollow membrane sacs are known as **vesicles**. This type of structure serves to transport substances within cells and in the blood (see p. 278).

The separation of oil and water (**B**) can be prevented by adding a strongly amphipathic substance. During shaking, a more or less stable **emulsion** then forms, in which the surface of the oil drops is occupied by amphipathic molecules that provide it with polar properties externally. The emulsification of fats in food by bile acids and phospholipids is a vital precondition for the digestion of fats (see p. 314).



## Acids and bases

### A. Acids and bases ●

In general, **acids** are defined as substances that can donate hydrogen ions (protons), while **bases** are compounds that accept protons.

Water enhances the acidic or basic properties of dissolved substances, as water itself can act as either an acid or a base. For example, when **hydrogen chloride** (HCl) is in aqueous solution, it donates protons to the solvent (**1**). This results in the formation of chloride ions ($Cl^-$) and protonated water molecules (**hydronium ions, $H_3O^+$**, usually simply referred to as $H^+$). The proton exchange between HCl and water is virtually quantitative: in water, HCl behaves as a *very strong acid* with a negative $pK_a$ value (see p. 18).

Bases such as **ammonia** ($NH_3$) take over protons from water molecules. As a result of this, **hydroxyl ions** ($OH^-$) and positively charged ammonium ions ($NH_4^+$, **3**) form. Hydronium and hydroxyl ions, like other ions, exist in water in hydrated rather than free form (see p. 26).

Acid–base reactions always involve *pairs* of **acids** and the associated **conjugated bases** (see p. 18). The stronger the acid or base, the *weaker* the conjugate base or acid, respectively. For example, the very strongly acidic hydrogen chloride belongs to the very weakly basic chloride ion (**1**). The weakly acidic ammonium ion is conjugated with the moderately strong base ammonia (**3**).

The equilibrium constant K for the acid—base reaction between $H_2O$ molecules (**2**) is very small. At 25 °C,

$$K = [H^+]\ [OH^-] / [H_2O] = 2\ \ 10^{-16}\ \text{mol}\ \ L^{-1}$$

In pure water, the concentration $[H_2O]$ is practically constant at 55 mol $L^{-1}$. Substituting this value into the equation, it gives:

$$K_w = [H^+]\ [OH^-] = 1\ \ 10^{-14}\ \text{mol}\ \ L^{-1}$$

The product $[H^+]\ [OH^-]$—the **ion product** of water—is constant even when additional acid–base pairs are dissolved in the water. At 25 °C, pure water contains $H^+$ and $OH^-$ at concentrations of $1\ \ 10^{-7}$ mol $L^{-1}$ each; it is **neutral** and has a pH value of exactly 7.

### B. pH values in the organism ◑

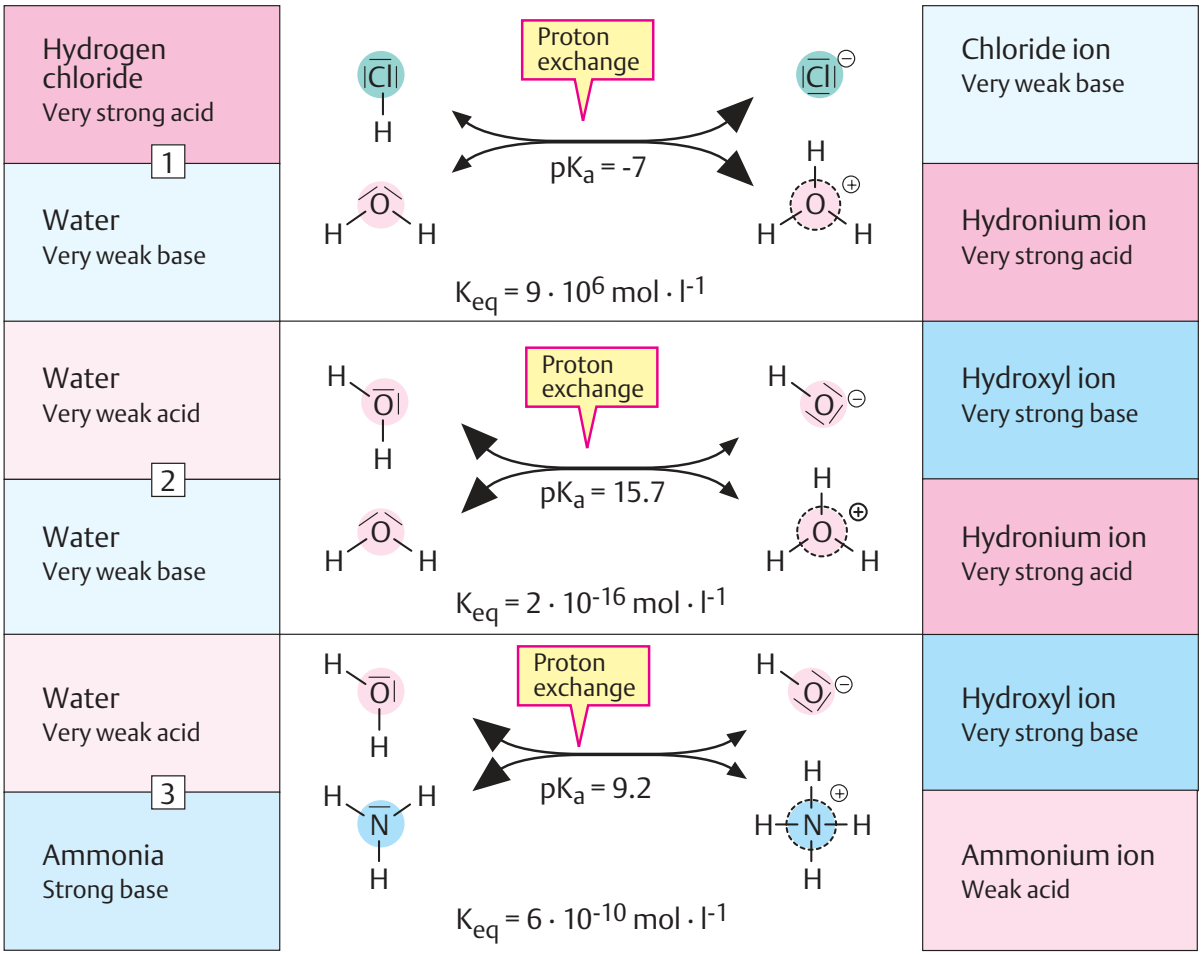
pH values in the cell and in the extracellular fluid are kept constant within narrow limits. In the blood, the pH value normally ranges only between 7.35 and 7.45 (see p. 288). This corresponds to a maximum change in the $H^+$ concentration of ca. 30%. The pH value of cytoplasm is slightly lower than that of blood, at 7.0–7.3. In lysosomes (see p. 234; pH 4.5–5.5), the $H^+$ concentration is several hundred times higher than in the cytoplasm. In the lumen of the gastrointestinal tract, which forms part of the outside world relative to the organism, and in the body's excretion products, the pH values are more variable. Extreme values are found in the stomach (ca. 2) and in the small bowel (> 8). Since the kidney can excrete either acids or bases, depending on the state of the metabolism, the pH of urine has a particularly wide range of variation (4.8–7.5).

### C. Buffers ●

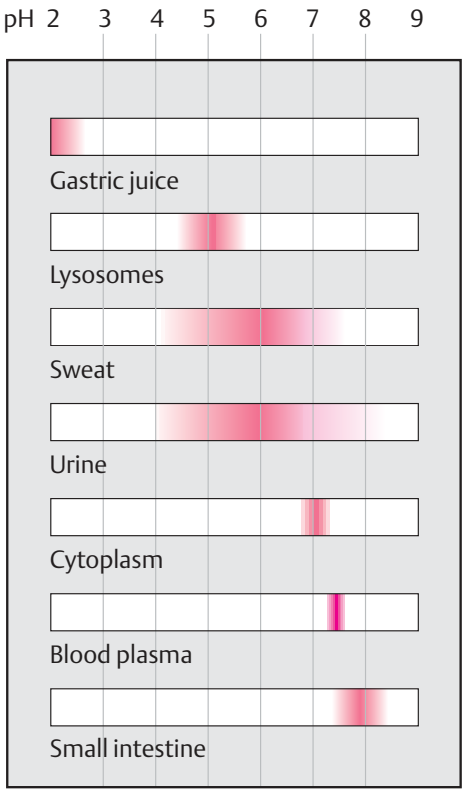
Short–term pH changes in the organism are cushioned by **buffer systems**. These are mixtures of a weak acid, HB, with its conjugate base, $B^-$, or of a weak base with its conjugate acid. This type of system can neutralize both hydronium ions and hydroxyl ions.

In the first case (left), the base ($B^-$) binds a large proportion of the added protons ($H^+$) and HB and water are formed. If hydroxyl ions ($OH^-$) are added, they react with HB to give $B^-$ and water (right). In both cases, it is primarily the $[HB]/[B^-]$ ratio that shifts, while the pH value only changes slightly. The **titration curve** (top) shows that buffer systems are most effective at the pH values that correspond to the $pK_a$ value of the acid. This is where the curve is at its steepest, so that the pH change, $\Delta$pH, is at its smallest with a given increase $\Delta c$ in $[H^+]$ or $[OH^-]$. In other words, the **buffer capacity** $\Delta c / \Delta$pH is highest at the $pK_a$ value.

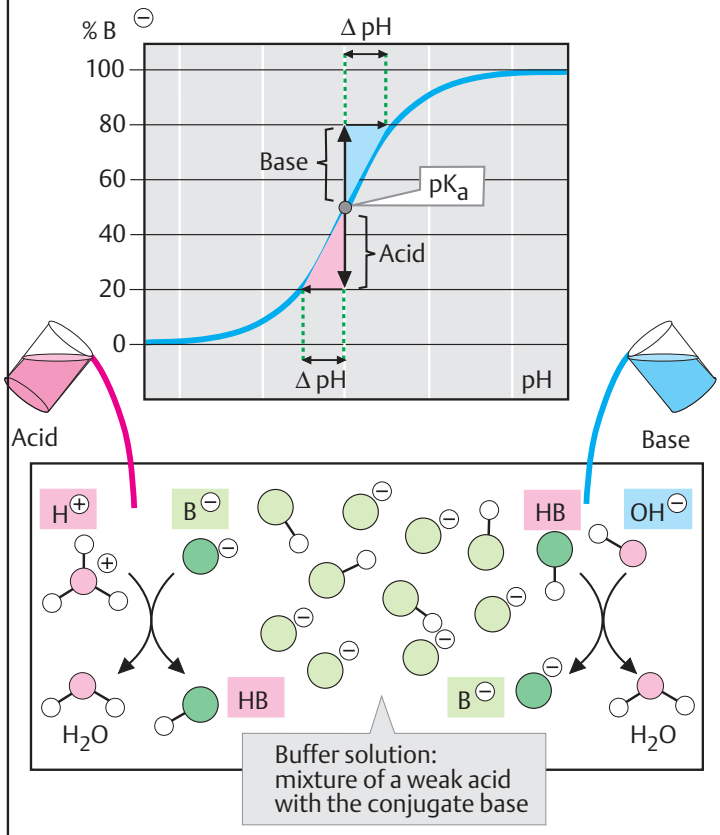
## A. Acids and bases




## B. pH values in the body




## C. Buffers



## Redox processes

### A. Redox reactions ●

Redox reactions are chemical changes in which electrons are transferred from one reaction partner to another (**1**; see also p. 18). Like acid–base reactions (see p. 30), redox reactions always involve *pairs* of compounds. A pair of this type is referred to as a **redox system** (**2**). The essential difference between the two components of a redox system is the number of electrons they contain. The more electronrich component is called the **reduced form** of the compound concerned, while the other one is referred to as the **oxidized form**. The reduced form of one system (the **reducing agent**) donates electrons to the oxidized form of another one (the **oxidizing agent**). In the process, the reducing agent becomes oxidized and the oxidizing agent is reduced (**3**). Any given reducing agent can reduce only certain other redox systems. On the basis of this type of observation, redox systems can be arranged to form what are known as **redox series** (**4**).

The position of a system within one of these series is established by its **redox potential E** (see p. 18). The redox potential has a sign; it can be more negative or more positive than a reference potential arbitrarily set at zero (the normal potential of the system [2 $H^+/H_2$]). In addition, E depends on the concentrations of the reactants and on the reaction conditions (see p. 18). In redox series (**4**), the systems are arranged according to their increasing redox potentials. Spontaneous electron transfers are only possible if the redox potential of the donor is *more negative* than that of the acceptor (see p. 18).

### B. Reduction equivalents ◑

In redox reactions, protons ($H^+$) are often transferred along with electrons ($e^-$), or protons may be released. The combinations of electrons and protons that occur in redox processes are summed up in the term **reduction equivalents**. For example, the combination 1 $e^-$/1 $H^+$ corresponds to a hydrogen *atom,* while 2 $e^-$ and 2 $H^+$ together produce a hydrogen *molecule.* However, this does not mean that atomic or molecular hydrogen is actually transferred from one molecule to the other (see below). Only the combination 2 $e^-$/1 $H^+$, the **hydride ion**, is transferred as a unit.

### C. Biological redox systems ◑

In the cell, redox reactions are catalyzed by enzymes, which work together with soluble or bound redox cofactors.

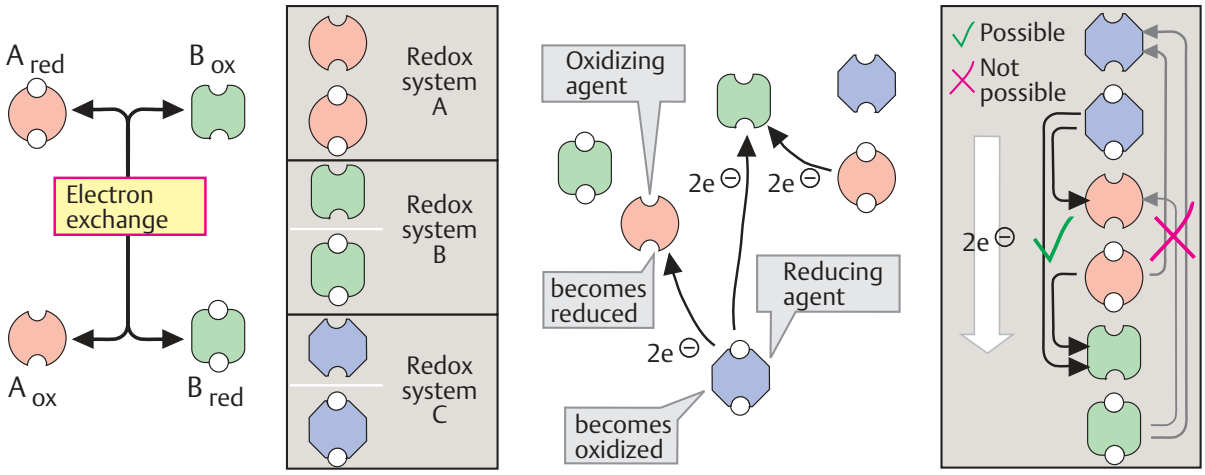
Some of these factors contain **metal ions** as redox-active components. In these cases, it is usually single electrons that are transferred, with the metal ion changing its valency. Unpaired electrons often occur in this process, but these are located in d orbitals (see p. 2) and are therefore less dangerous than single electrons in non-metal atoms ("free radicals"; see below).

We can only show here a few examples from the many organic redox systems that are found. In the complete reduction of the **flavin coenzymes** FMN and FAD (see p. 104), 2 $e^-$ and 2 $H^+$ are transferred. This occurs in two separate steps, with a *semiquinone radical* appearing as an intermediate. Since organic radicals of this type can cause damage to biomolecules, flavin coenzymes never occur freely in solution, but remain firmly bound in the interior of proteins.

In the reduction or oxidation of **quinone/quinol systems**, free radicals also appear as intermediate steps, but these are less reactive than flavin radicals. Vitamin E, another quinone-type redox system (see p. 104), even functions as a radical scavenger, by delocalizing unpaired electrons so effectively that they can no longer react with other molecules.

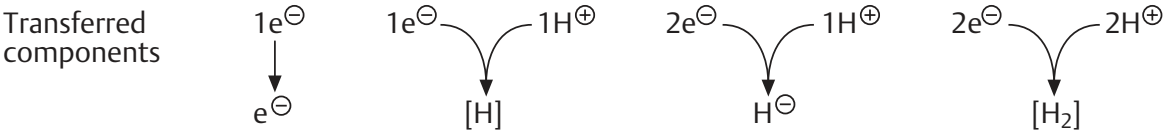
The **pyridine nucleotides** $NAD^+$ and $NADP^+$ always function in unbound form. The oxidized forms contain an aromatic nicotinamide ring in which the positive charge is delocalized. The right-hand example of the two *resonance structures* shown contains an electron-poor, positively charged C atom at the *para* position to nitrogen. If a **hydride ion** is added at this point (see above), the reduced forms NADH or NADPH arise. No radical intermediate steps occur. Because a proton is released at the same time, the reduced pyridine nucleotide coenzymes are correctly expressed as NAD(P)H+$H^+$.

## A. Redox reactions

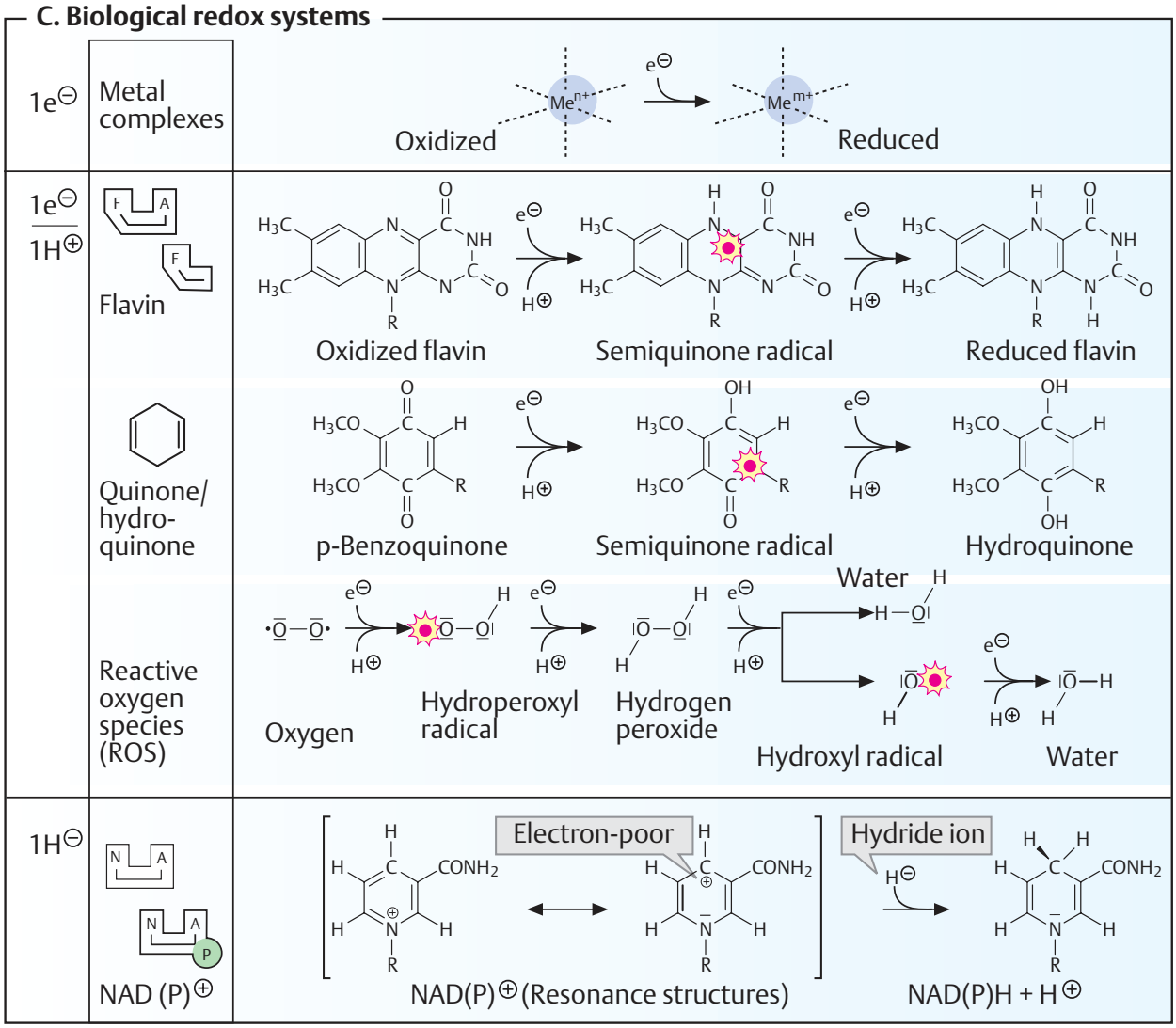



**1.** Principle **2.** Redox systems **3.** Possible electron transfers **4.** Redox series

## B. Reducing equivalents




## C. Biological redox systems



## Overview

The **carbohydrates** are a group of naturally occurring carbonyl compounds (aldehydes or ketones) that also contain several hydroxyl groups. The carbohydrates include **single sugars (monosaccharides)** and their polymers, the **oligosaccharides** and **polysaccharides**.

### A. Carbohydrates: overview ●

Polymeric carbohydrates–above all starch, as well as some disaccharides–are important (but not essential) **components of food** (see p. 360). In the gut, they are broken down into monosaccharides and resorbed in this form (see p. 272). The form in which carbohydrates are distributed by the blood of vertebrates is *glucose* ("blood sugar"). This is taken up by the cells and either broken down to obtain energy (glycolysis) or converted into other metabolites (see pp. 150–159). Several organs (particularly the liver and muscles) store *glycogen* as a polymeric **reserve carbohydrate** (right; see p. 156). The glycogen molecules are covalently bound to a protein, *glycogenin*. Polysaccharides are used by many organisms as **building materials**. For example, the cell walls of bacteria contain *murein* as a stabilizing component (see p. 40), while in plants *cellulose* and other polysaccharides fulfill this role (see p. 42). Oligomeric or polymeric carbohydrates are often covalently bound to lipids or proteins. The **glycolipids** and **glycoproteins** formed in this way are found, for example, in cell membranes (center). Glycoproteins also occur in the blood in solute form (plasma proteins; see p. 276) and, as components of *proteoglycans,* form important constituents of the intercellular substance (see p. 346).

### B. Monosaccharides: structure ◑

The most important natural monosaccharide, **D-glucose**, is an aliphatic aldehyde with six C atoms, five of which carry a hydroxyl group (**1**). Since C atoms 2 to 5 represent chiral centers (see p. 8), there are 15 further isomeric *aldohexoses* in addition to D-glucose, although only a few of these are important in nature (see p. 38). Most natural monosaccharides have the same configuration at C-5 as D-glyceraldehyde–they belong to the D **series**.

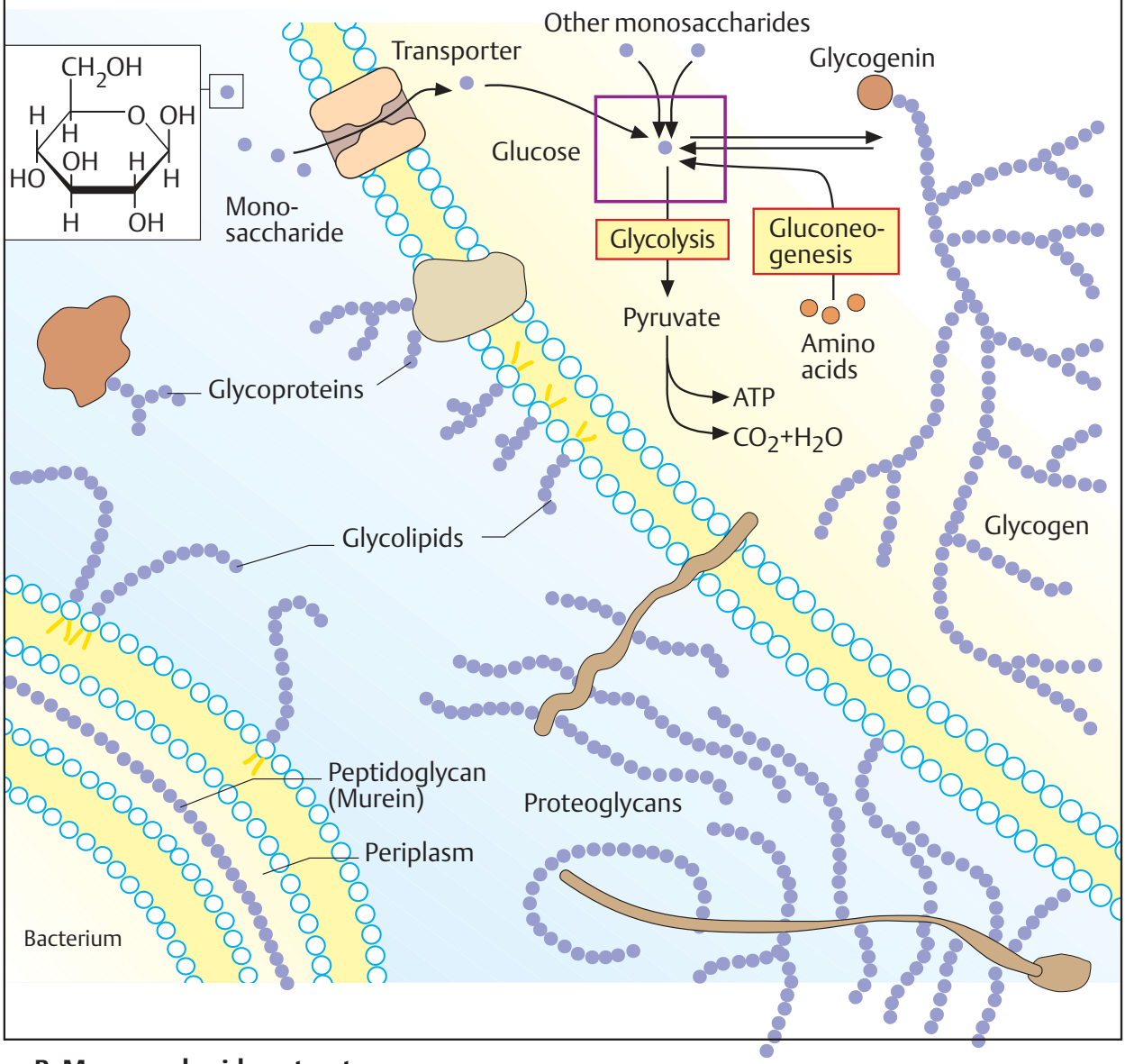
The open-chained form of glucose shown in (**1**) is found in neutral solution in less than 0.1% of the molecules. The reason for this is an intramolecular reaction in which one of the OH groups of the sugar is added to the aldehyde group of the *same* molecule (**2**). This gives rise to a cyclic **hemiacetal** (see p. 10). In aldohexoses, the hydroxy group at C-5 reacts preferentially, and a six-membered pyran ring is formed. Sugars that contain this ring are called **pyranoses**. By contrast, if the OH group at C-4 reacts, a five-part furan ring is formed. In solution, *pyranose* forms and *furanose* forms are present in equilibrium with each other and with the open-chained form, while in glucose polymers only the pyranose form occurs.

The **Haworth projection** (**2**) is usually used to depict sugars in the cyclic form, with the ring being shown in perspective as viewed from above. Depending on the configuration, the substituents of the chiral C atoms are then found above or below the ring. OH groups that lie on the *right* in the Fischer projection (**1**) appear *under* the ring level in the Haworth projection, while those on the *left* appear *above* it.

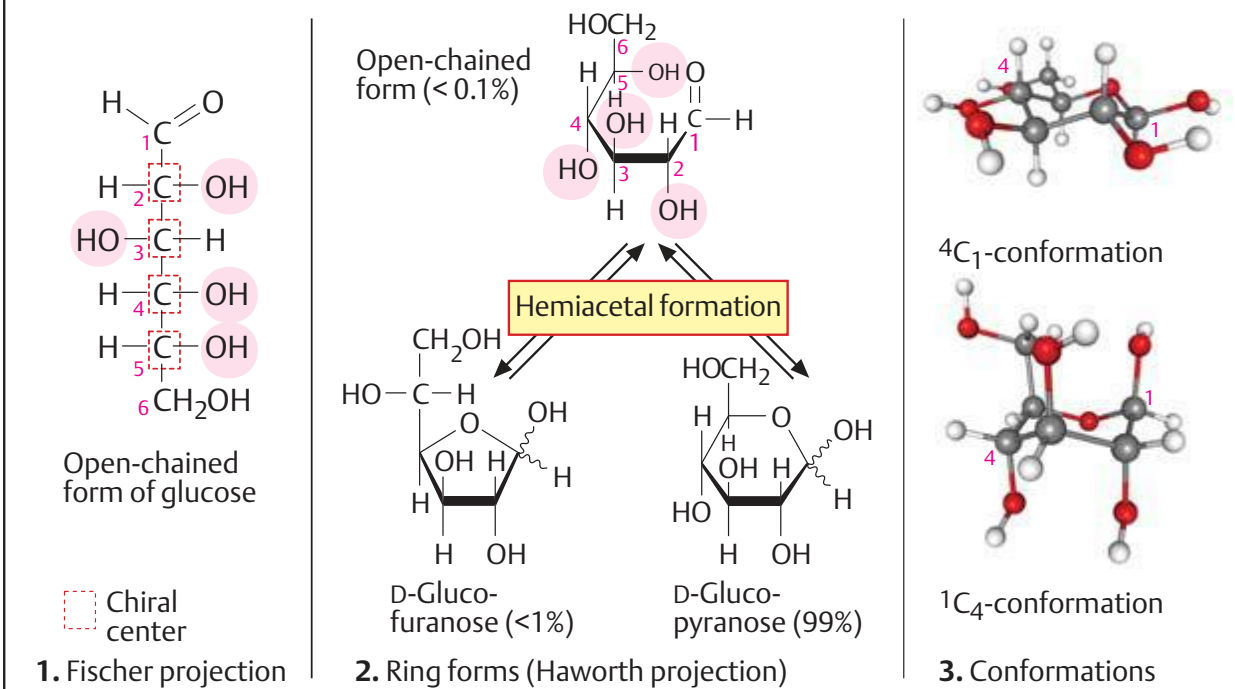
As a result of hemiacetal formation, an additional chiral center arises at C-1, which can be present in both possible configurations (anomers) (see p. 8). To emphasize this, the corresponding bonds are shown here using wavy lines.

The Haworth formula does not take account of the fact that the pyran ring is not plain, but usually has a *chair conformation*. In **B3**, two frequent conformations of D-glucopyranose are shown as ball-and-stick models. In the $^1C_4$ conformation (bottom), most of the OH groups appear vertical to the ring level, as in the Haworth projection (**axial** or **a** position). In the slightly more stable $^4C_1$ conformation (top), the OH groups take the **equatorial** or **e** position. At room temperature, each form can change into the other, as well as into other conformations.

## A. Carbohydrates: overview




## B. Monosaccharides: structure



## Chemistry of sugars

### A. Reactions of the monosaccharides ◑

The sugars (monosaccharides) occur in the metabolism in many forms (derivatives). Only a few important conversion reactions are discussed here, using **D**-glucose as an example.

**1. Mutarotation.** In the cyclic form, as opposed to the open-chain form, aldoses have a chiral center at C-1 (see p. 34). The corresponding isomeric forms are called **anomers**. In the β-anomer (center left), the OH group at C-1 (the anomeric OH group) and the $CH_2OH$ group lie on the *same* side of the ring. In the α-anomer (right), they are on different sides. The reaction that interconverts anomers into each other is known as *mutarotation* (**B**).

**2. Glycoside formation.** When the anomeric OH group of a sugar reacts with an alcohol, with elimination of water, it yields an *O–glycoside* (in the case shown, α–methylglucoside). The glycosidic bond is not a normal ether bond, because the OH group at C-1 has a hemiacetal quality. Oligosaccharides and polysaccharides also contain *O*-glycosidic bonds. Reaction of the anomeric OH group with an $NH_2$ or NH group yields an *N-glycoside* (not shown). *N*-glycosidic bonds occur in nucleotides (see p. 80) and in glycoproteins (see p. 44), for example.

**3. Reduction and oxidation.** Reduction of the anomeric center at C-1 of glucose (2) produces the sugar alcohol *sorbitol*. Oxidation of the aldehyde group at C-1 gives the intramolecular ester (lactone) of *gluconic acid* (a glyconic acid). Phosphorylated gluconolactone is an intermediate of the pentose phosphate pathway (see p. 152). When glucose is oxidized at C-6, *glucuronic acid* (a glycuronic acid) is formed. The strongly polar glucuronic acid plays an important role in biotransformations in the liver (see pp. 194, 316).

**4. Epimerization.** In weakly alkaline solutions, glucose is in equilibrium with the ketohexose D-*fructose* and the aldohexose D-*mannose,* via an enediol intermediate (not shown). The only difference between glucose and mannose is the configuration at C-2. Pairs of sugars of this type are referred to as *epimers*, and their interconversion is called *epimerization*.

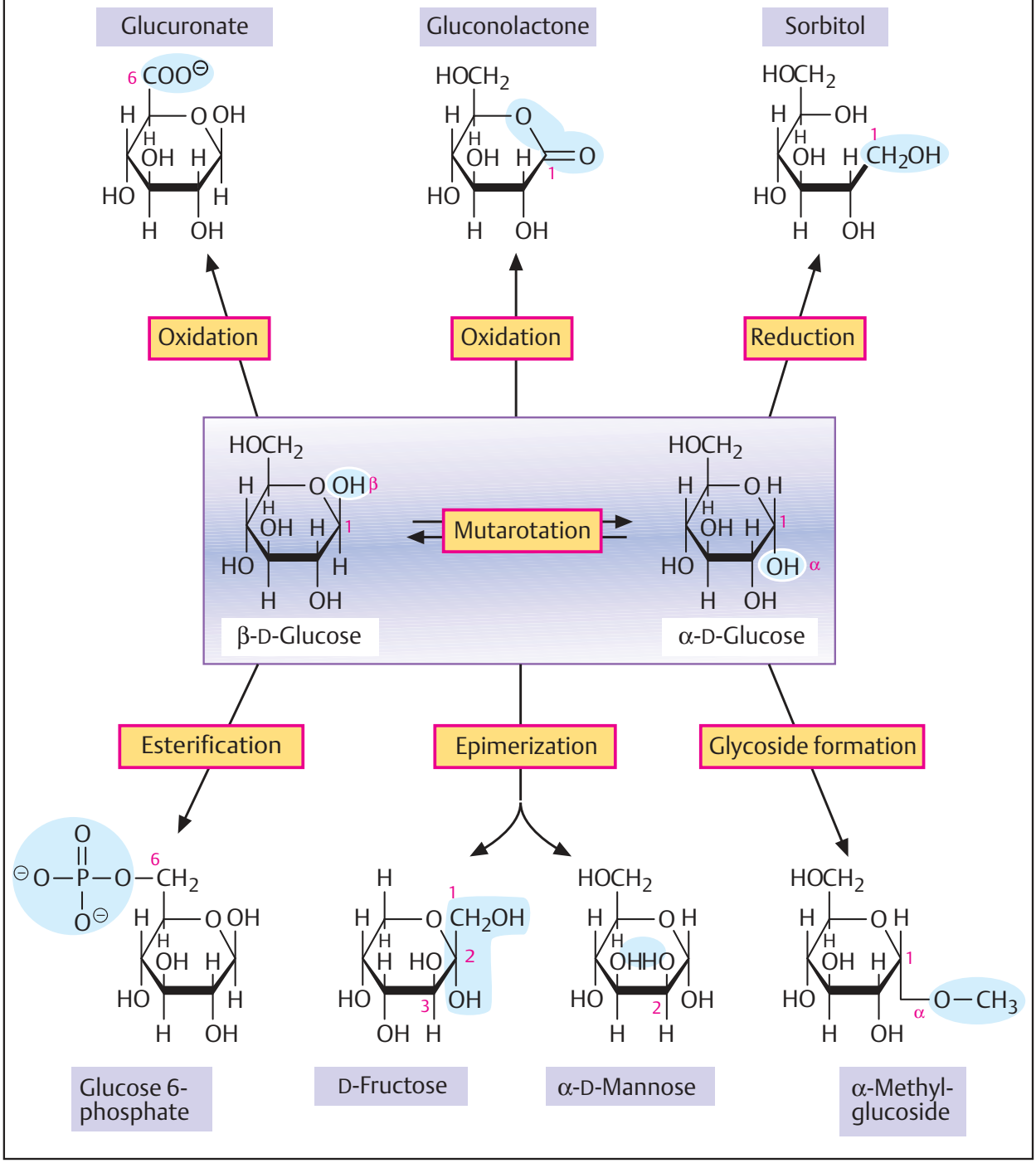
**5. Esterification.** The hydroxyl groups of monosaccharides can form *esters* with acids. In metabolism, phosphoric acid esters such as *glucose 6-phosphate* and *glucose 1-phosphate* (6) are particularly important.

### B. Polarimetry, mutarotation ○

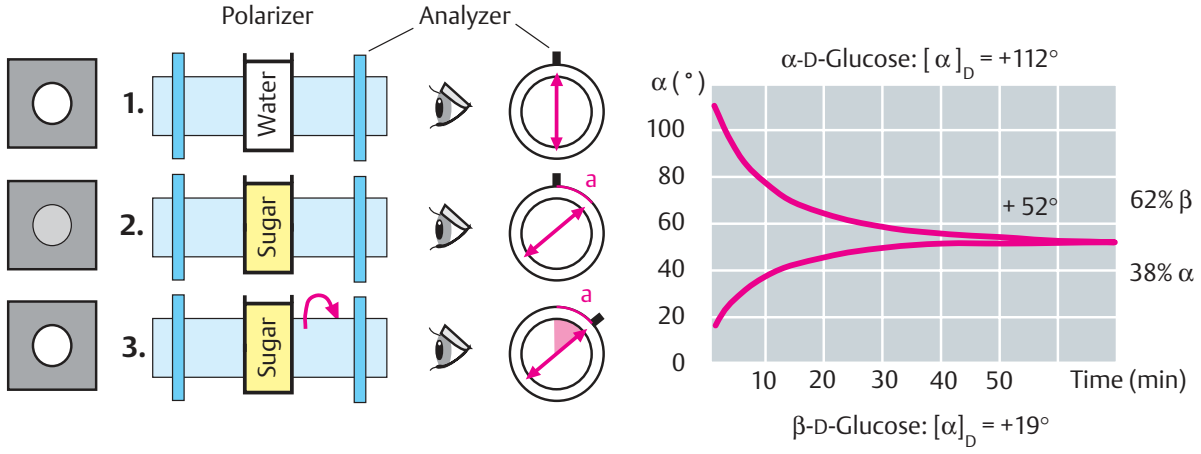
Sugar solutions can be analyzed by **polarimetry**, a method based on the interaction between chiral centers and linearly polarized light—i. e., light that oscillates in only *one* plane. It can be produced by passing normal light through a special filter (a **polarizer**). A second polarizing filter of the same type (the **analyzer**), placed behind the first, only lets the polarized light pass through when the polarizer and the analyzer are in alignment. In this case, the field of view appears bright when one looks through the analyzer (**1**). Solutions of chiral substances rotate the plane of polarized light by an angle α either to the left or to the right. When a solution of this type is placed between the polarizer and the analyzer, the field of view appears darker (**2**). The angle of rotation, α, is determined by turning the analyzer until the field of view becomes bright again (**3**). A solution's **optical rotation** depends on the type of chiral compound, its concentration, and the thickness of the layer of the solution. This method makes it possible to determine the sugar content of wines, for example.

Certain procedures make it possible to obtain the α and β anomers of glucose in pure form. A 1-molar solution of α-D-glucose has a rotation value $[\alpha]_D$ of +112°, while a corresponding solution of β-D-glucose has a value of +19°. These values change spontaneously, however, and after a certain time reach the same end point of +52°. The reason for this is that, in solution, **mutarotation** leads to an equilibrium between the α and β forms in which, independently of the starting conditions, 62% of the molecules are present in the β form and 38% in the α form.

## A. Reactions of the monosaccharides




## B. Polarimetry, mutarotation



## Monosaccharides and disaccharides

### A. Important monosaccharides ◑

Only the most important of the large number of naturally occurring **monosaccharides** are mentioned here. They are classified according to the number of C atoms (into pentoses, hexoses, etc.) and according to the chemical nature of the carbonyl function into aldoses and ketoses.

The best-known **aldopentose** (**1**), D-*ribose*, is a component of RNA and of nucleotide coenzymes and is widely distributed. In these compounds, ribose always exists in the furanose form (see p. 34). Like ribose, D-*xylose* and L-*arabinose* are rarely found in free form. However, large amounts of both sugars are found as constituents of polysaccharides in the walls of plant cells (see p. 42).

The most important of the **aldohexoses** (**1**) is D-glucose. A substantial proportion of the biomass is accounted for by glucose polymers, above all cellulose and starch. Free D-glucose is found in plant juices ("grape sugar") and as "blood sugar" in the blood of higher animals. As a constituent of lactose (milk sugar), D-galactose is part of the human diet. Together with D-mannose, galactose is also found in glycolipids and glycoproteins (see p. 44).

Phosphoric acid esters of the **ketopentose** D-*ribulose* (**2**) are intermediates in the pentose phosphate pathway (see p. 152) and in photosynthesis (see p. 128). The most widely distributed of the **ketohexoses** is D-*fructose*. In free form, it is present in fruit juices and in honey. Bound fructose is found in sucrose (**B**) and plant polysaccharides (e. g., inulin).

In the **deoxyaldoses** (**3**), an OH group is replaced by a hydrogen atom. In addition to 2-*deoxy-D-ribose*, a component of DNA (see p. 84) that is reduced at C-2, L-fucose is shown as another example of these. Fucose, a sugar in the λ series (see p. 34) is reduced at C-6.

The **acetylated amino sugars** *N-acetyl-D-glucosamine* and *N-acetyl-D-Galactosamine* (**4**) are often encountered as components of glycoproteins.

*N-acetylneuraminic acid* (sialic acid, **5**), is a characteristic component of glycoproteins. Other **acidic monosaccharides** such as D-*glucuronic acid*, D-*galacturonic acid*, and *liduronic acid*, are typical constituents of the glycosaminoglycans found in connective tissue.

**Sugar alcohols** (**6**) such as *sorbitol* and *mannitol* do not play an important role in animal metabolism.

### B. Disaccharides ◑

When the anomeric hydroxyl group of one monosaccharide is bound glycosidically with one of the OH groups of another, a **disaccharide** is formed. As in all glycosides, the glycosidic bond does *not* allow mutarotation. Since this type of bond is formed stereospecifically by enzymes in natural disaccharides, they are only found in *one* of the possible configurations (α or β).

**Maltose** (**1**) occurs as a breakdown product of the starches contained in malt ("malt sugar"; see p. 148) and as an intermediate in intestinal digestion. In maltose, the anomeric OH group of one glucose molecule has an α-glycosidic bond with C-4 in a second glucose residue.

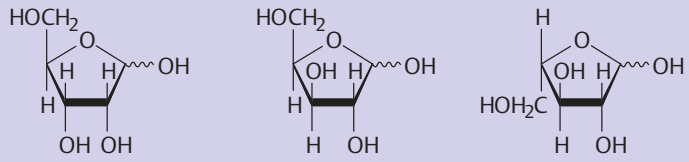
**Lactose** ("milk sugar," **2**) is the most important carbohydrate in the milk of mammals. Cow's milk contains 4.5% lactose, while human milk contains up to 7.5%. In lactose, the anomeric OH group of galactose forms a β-glycosidic bond with C-4 of a glucose. The lactose molecule is consequently elongated, and both of its pyran rings lie in the same plane.

**Sucrose** (**3**) serves in plants as the form in which carbohydrates are transported, and as a soluble carbohydrate reserve. Humans value it because of its intensely sweet taste. Sources used for sucrose are plants that contain particularly high amounts of it, such as sugar cane and sugar beet (*cane sugar, beet sugar*). Enzymatic hydrolysis of sucrose-containing flower nectar in the digestive tract of bees—catalyzed by the enzyme *invertase*—produces **honey**, a mixture of glucose and fructose. In sucrose, the two anomeric OH groups of glucose and fructose have a glycosidic bond; sucrose is therefore one of the non-reducing sugars.

## A. Important monosaccharides

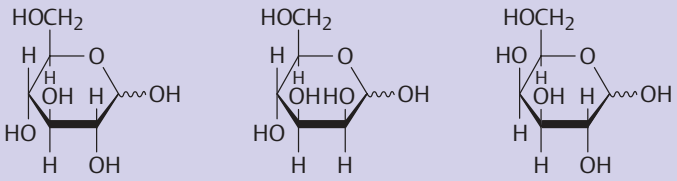
### ① Aldoses

D-Ribose (Rib) | D-Xylose (Xyl) | L-Arabinose (Ara)



Pentoses

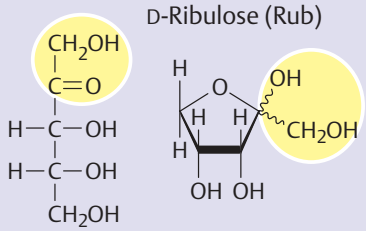
D-Glucose (Glc) | D-Mannose (Man) | D-Galactose (Gal)



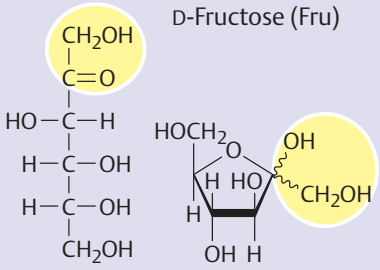
Hexoses

### ② Ketoses

D-Ribulose (Rub)

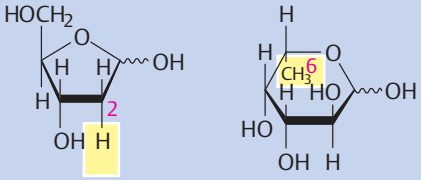


D-Fructose (Fru)



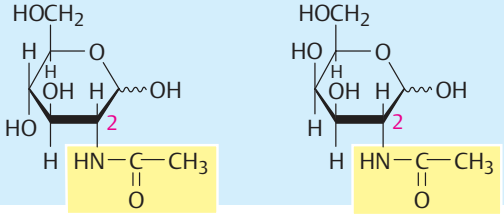
### ③ Deoxyaldoses

2-Deoxy-D-ribose (dRib) | L-Fucose (Fuc)



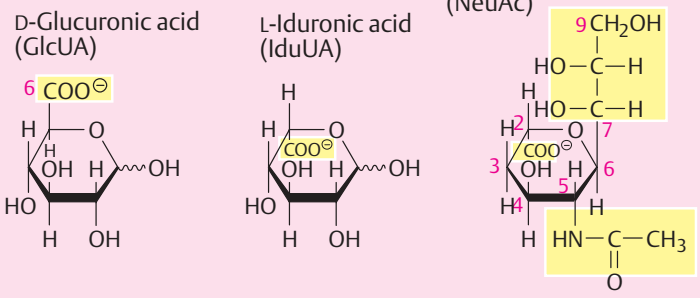
### ④ Acetylated amino sugars

*N*-Acetyl-D-glucosamine (GlcNAc) | *N*-Acetyl-D-galactosamine (GalNAc)



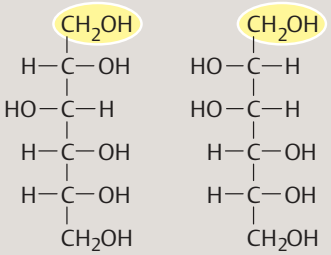
### ⑤ Acidic monosaccharides

D-Glucuronic acid (GlcUA) | L-Iduronic acid (IduUA) | *N*-Acetylneuraminic acid (NeuAc)

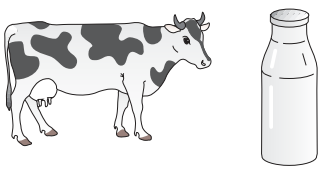


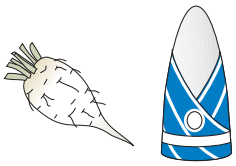
### ⑥ Sugar alcohols (alditoles)

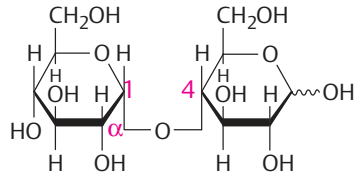
D-Sorbitol | D-Mannitol



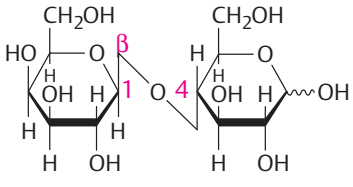
## B. Disaccharides



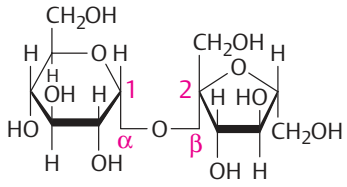




**1.** Maltose
α-D-Glucopyranosyl-(1→4)-D-glucopyranose



**2.** Lactose
β-D-Galactopyranosyl-(1→4)-D-glucopyranose



**3.** Sucrose
α-D-Glucopyranosyl-(1↔2)-β-D-fructofuranoside

## Polysaccharides: overview

Polysaccharides are ubiquitous in nature. They can be classified into three separate groups, based on their different *functions*. **Structural polysaccharides** provide mechanical stability to cells, organs, and organisms. **Waterbinding polysaccharides** are strongly hydrated and prevent cells and tissues from drying out. Finally, **reserve polysaccharides** serve as carbohydrate stores that release monosaccharides as required. Due to their polymeric nature, reserve carbohydrates are osmotically less active, and they can therefore be stored in large quantities within the cell.

### A. Polysaccharides: structure ◑

Polysaccharides that are formed from only *one* type of monosaccharide are called **homoglycans**, while those formed from different sugar constituents are called **heteroglycans**. Both forms can exist as either linear or branched chains.

A section of a **glycogen** molecule is shown here as an example of a branched homoglycan. Amylopectin, the branched component of vegetable starch (see p. 42), has a very similar structure. Both molecules mainly consist of α1→4-linked glucose residues. In glycogen, on average every 8th to 10th residue carries —via an α1→6 bond—another 1,4-linked chain of glucose residues. This gives rise to branched, tree-like structures, which in animal glycogen are covalently bound to a protein, *glycogenin* (see p. 156).

The linear heteroglycan **murein**, a structural polysaccharide that stabilizes the cell walls of bacteria, has a more complex structure. Only a short segment of this thread-like molecule is shown here. In murein, two different components, both β1→4-linked, alternate: *N-acetylglucosamine* (GlcNAc) and *N-acetylmuraminic acid* (MurNAc), a lactic acid ether of *N*-acetylglucosamine. *Peptides* are bound to the carboxyl group of the lactyl groups, and attach the individual strands of murein to each other to form a three-dimensional network (not shown). Synthesis of the network-forming peptides in murein is inhibited by *penicillin* (see p. 254).

### B. Important polysaccharides ◑

The table gives an overview of the composition and make-up both of the glycans mentioned above and of several more.

In addition to murein, bacterial polysaccharides include **dextrans**—glucose polymers that are mostly α1→6-linked and α1→3-branched. In water, dextrans form viscous slimes or gels that are used for chromatographic separation of macromolecules after chemical treatment (see p. 78). Dextrans are also used as components of blood plasma substitutes (plasma expanders) and foodstuffs.

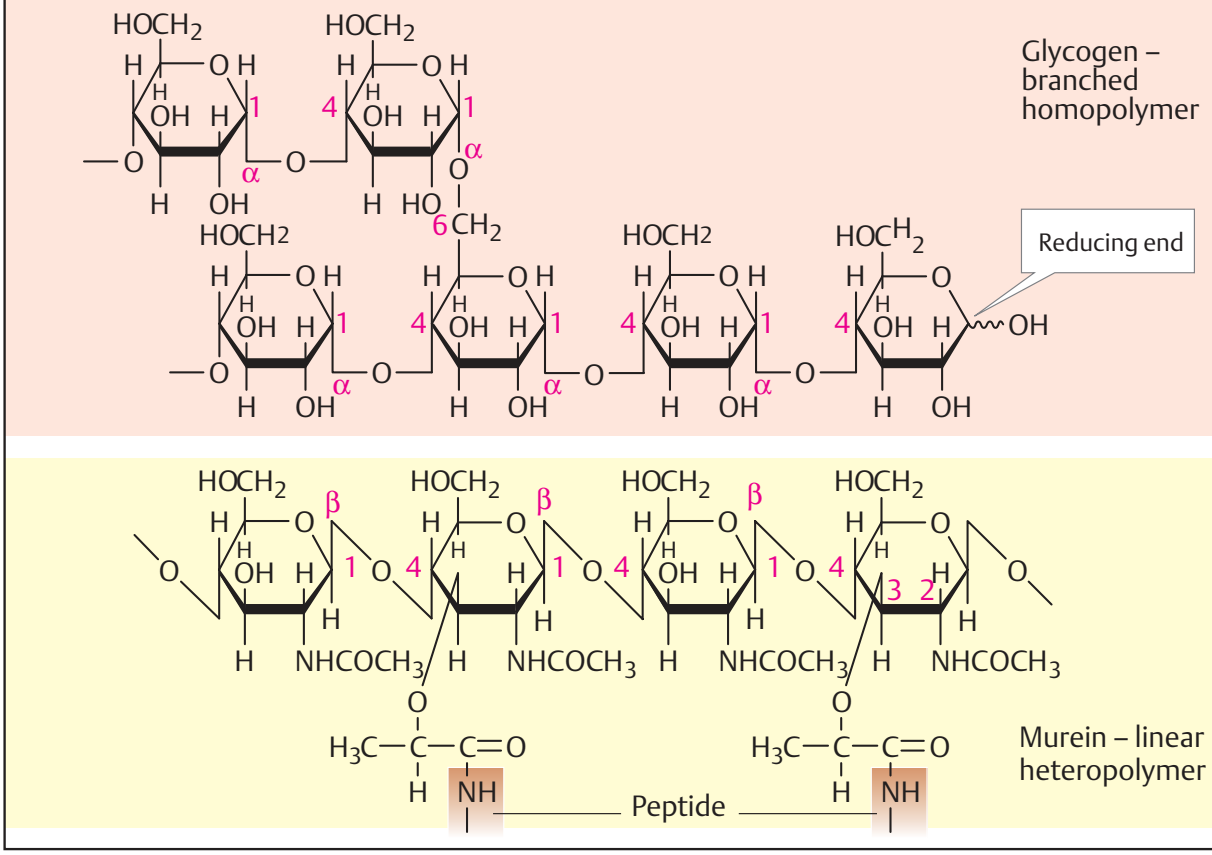
Carbohydrates from algae (e.g., **agarose** and **carrageenan**) can also be used to produce gels. Agarose has been used in microbiology for more than 100 years to reinforce culture media ("agar-agar"). Algal polysaccharides are also added to cosmetics and ready-made foods to modify the consistency of these products.

The **starches**, the most important vegetable reserve carbohydrate and polysaccharides from plant cell walls, are discussed in greater detail on the following page. **Inulin**, a fructose polymer, is used as a starch substitute in diabetics' dietary products (see p. 160). In addition, it serves as a test substance for measuring renal clearance (see p. 322).

**Chitin**, a homopolymer from β1→4-linked *N*-acetylglucosamine, is the most important structural substance in insect and crustacean shells, and is thus the most common animal polysaccharide. It also occurs in the cell wall of fungi.

**Glycogen**, the reserve carbohydrate of higher animals, is stored in the liver and musculature in particular (**A**, see pp. 156, 336). The formation and breakdown of glycogen are subject to complex regulation by hormones and other factors (see p. 120).

## A. Polysaccharides: structure




## B. Important polysaccharides

| Poly-saccharide | Mono-saccharide 1 | Mono-saccharide 2 | Linkage | Branch-ing | Occurrence | Function |
|---|---|---|---|---|---|---|
| **Bacteria** | | | | | | |
| Murein | D-GlcNAc | D-MurNAc[1)] | β 1 →4 | — | Cell wall | SC |
| Dextran | D-Glc | — | α 1 →6 | α 1→3 | Slime | WB |
| **Plants** | | | | | | |
| Agarose | D-Gal | L-aGal[2)] | β 1 →4 | β 1→3 | Red algae (agar) | WB |
| Carrageenan | D-Gal | — | β 1 →3 | α 1→4 | Red algae | WB |
| Cellulose | D-Glc | — | β 1 →4 | — | Cell wall | SC |
| Xyloglucan | D-Glc | D-Xyl (D-Gal, L-Fuc) | β 1 →4 | β 1→6 (β 1→2) | Cell wall (Hemicellulose) | SC |
| Arabinan | L-Ara | — | α 1 →5 | α 1→3 | Cell wall (pectin) | SC |
| Amylose | D-Glc | — | α 1 →4 | — | Amyloplasts | RC |
| Amylopectin | D-Glc | — | α 1 →4 | α 1→6 | Amyloplasts | RC |
| Inulin | D-Fru | | β 2 →1 | — | Storage cells | RC |
| **Animals** | | | | | | |
| Chitin | D-GlcNAc | — | β 1 →4 | — | Insects, crabs | SK |
| Glycogen | D-Glc | — | α 1 →4 | α 1 →6 | Liver, muscle | RK |
| Hyaluronic acid | D-GlcUA | D-GlcNAc | β 1 →4<br>β 1 →3 | — | Connective tissue | SK,WB |

SC= structural carbohydrate, RC= reserve carbohydrate,
WB = water-binding carbohydrate; [1)] *N*-acetylmuramic acid, [2)] 3,6-anhydrogalactose

## Plant polysaccharides

Two glucose polymers of plant origin are of special importance among the polysaccharides: β1→4-linked polymer **cellulose** and **starch**, which is mostly α1→4-linked.

### A. Cellulose ◑

Cellulose, a linear homoglycan of β1→4-linked glucose residues, is the *most abundant organic substance* in nature. Almost half of the total biomass consists of cellulose. Some 40–50% of plant *cell walls* are formed by cellulose. The proportion of cellulose in *cotton fibers,* an important raw material, is 98%. Cellulose molecules can contain more than $10^4$ glucose residues (mass 1–2 $10^6$ Da) and can reach lengths of 6–8 μm.

Naturally occurring cellulose is *extremely mechanically stable* and is highly *resistant* to chemical and enzymatic hydrolysis. These properties are due to the conformation of the molecules and their supramolecular organization. The unbranched β1→4 linkage results in linear chains that are stabilized by hydrogen bonds within the chain and between neighboring chains (**1**). Already during biosynthesis, 50–100 cellulose molecules associate to form an **elementary fibril** with a diameter of 4 nm. About 20 such elementary fibrils then form a **microfibril** (**2**), which is readily visible with the electron microscope.

Cellulose microfibrils make up the basic framework of the **primary wall** of young plant cells (**3**), where they form a complex network with other polysaccharides. The linking polysaccharides include **hemicellulose**, which is a mixture of predominantly neutral heteroglycans (xylans, xyloglucans, arabinogalactans, etc.). Hemicellulose associates with the cellulose fibrils via noncovalent interactions. These complexes are connected by neutral and acidic **pectins**, which typically contain galacturonic acid. Finally, a collagen-related protein, **extensin**, is also involved in the formation of primary walls.

In the higher animals, including humans, cellulose is **indigestible**, but important as **roughage** (see p. 273). Many herbivores (e. g., the ruminants) have symbiotic unicellular organisms in their digestive tracts that break down cellulose and make it digestible by the host.

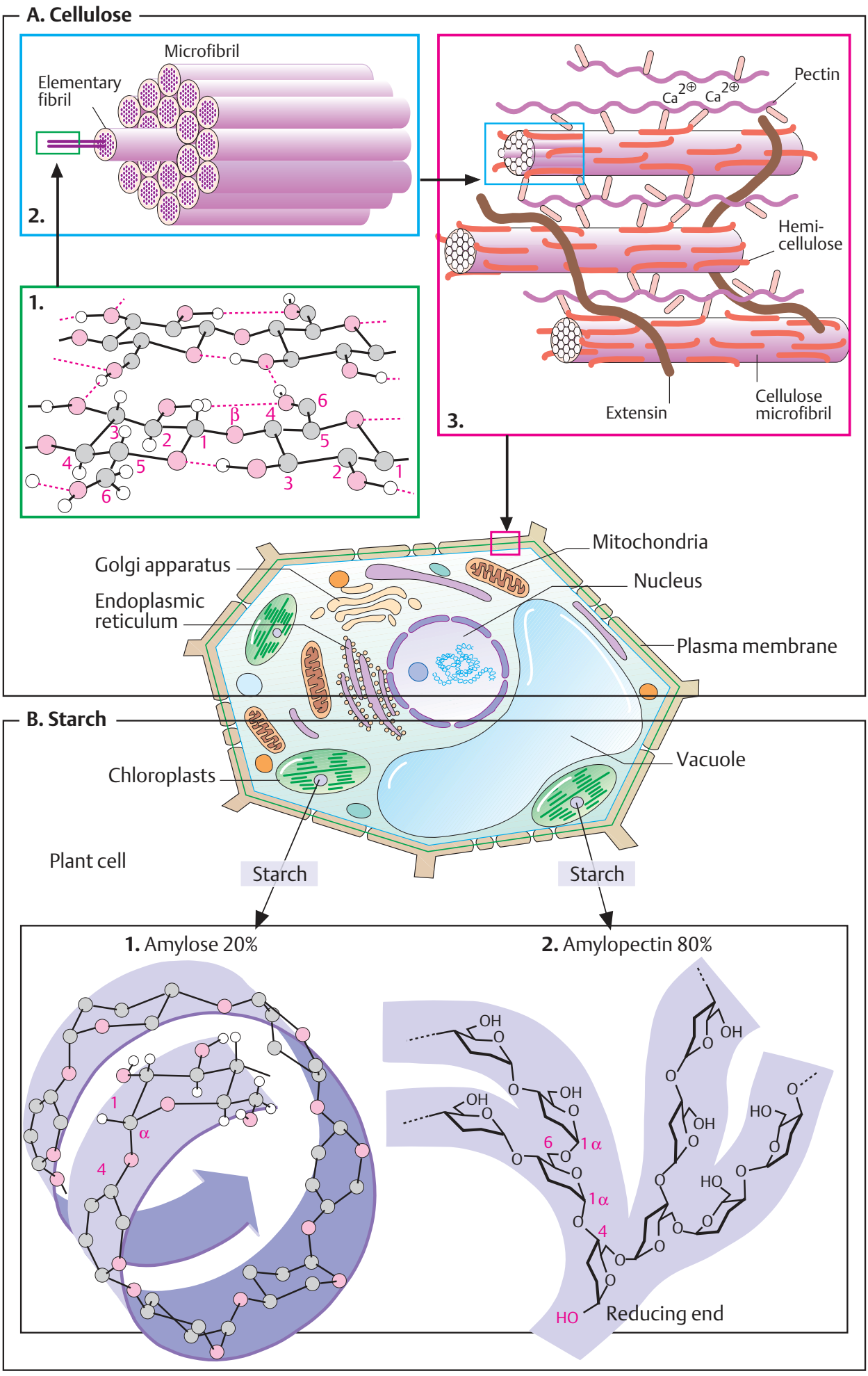
### B. Starch ◑

Starch, a **reserve polysaccharide** widely distributed in plants, is the *most important carbohydrate in the human diet.* In plants, starch is present in the chloroplasts in leaves, as well as in fruits, seeds, and tubers. The starch content is especially high in cereal grains (up to 75% of the dry weight), potato tubers (approximately 65%), and in other plant storage organs.

In these plant organs, starch is present in the form of microscopically small granules in special organelles known as **amyloplasts**. *Starch granules* are virtually insoluble in cold water, but swell dramatically when the water is heated. Some 15–25% of the starch goes into solution in colloidal form when the mixture is subjected to prolonged boiling. This proportion is called amylose ("soluble starch").

Amylose consists of *unbranched* α1→4-linked chains of 200–300 glucose residues. Due the α configuration at C-1, these chains form a *helix* with 6–8 residues per turn (**1**). The blue coloring that soluble starch takes on when iodine is added (the "iodine–starch reaction") is caused by the presence of these helices—the iodine atoms form chains inside the amylose helix, and in this largely nonaqueous environment take on a deep blue color. Highly branched polysaccharides turn brown or reddishbrown in the presence of iodine.

Unlike amylose, **amylopectin**, which is practically insoluble, is *branched*. On average, one in 20–25 glucose residues is linked to another chain via an α1→6 bond. This leads to an extended tree-like structure, which—like amylose—contains only *one* anomeric OH group (a "reducing end"). Amylopectin molecules can contain hundreds of thousands of glucose residues; their mass can be more than $10^8$ Da.



## Glycosaminoglycans and glycoproteins

### A. Hyaluronic acid ○

As constituents of proteoglycans (see p. 346), the glycosaminoglycans—a group of acidic heteropolysaccharides—are important structural elements of the extracellular matrix.

**Glycosaminoglycans** contain *amino sugars* as well as *glucuronic acid* and *iduronic acid* as characteristic components (see p. 38). In addition, most polysaccharides in this group are esterified to varying extents by sulfuric acid, increasing their acidic quality. Glycosaminoglycans can be found in free form, or as components of proteoglycans throughout the organism.

**Hyaluronic acid**, an unesterified glycosaminoglycan with a relatively simple structure, consists of disaccharide units in which *N-acetylglucosamine* and *glucuronic acid* are alternately β1→4-linked and β1→3-linked. Due to the unusual β1→3 linkage, hyaluronic acid molecules–which may contain several thousand monosaccharide residues—are coiled like a helix. Three disaccharide units form each turn of the helix. The outwardfacing hydrophilic carboxylate groups of the glucuronic acid residues are able to bind $Ca^{2+}$ ions. The **strong hydration** of these groups enables hyaluronic acid and other glycosaminoglycans to bind water up to 10 000 times their own volume in gel form. This is the function which hyaluronic acid has in the *vitreous body* of the eye, which contains approximately 1% hyaluronic acid and 98% water.

### B. Oligosaccharide in immunoglobulin G (IgG) ○

Many proteins on the surface of the plasma membrane, and the majority of secreted proteins, contain oligosaccharide residues that are post-translationally added to the endoplasmic reticulum and in the Golgi apparatus (see p. 230). By contrast, cytoplasmic proteins are rarely glycosylated. **Glycoproteins** can contain more than 50% carbohydrate; however, the proportion of protein is generally much greater.

As an example of the carbohydrate component of a glycoprotein, the structure of one of the oligosaccharide chains of immunoglobulin G (IgG; see p. 300) is shown here. The oligosaccharide has an *N-glycosidic* link to the amide group of an asparagine residue in the $F_c$ part of the protein. Its function is not known.

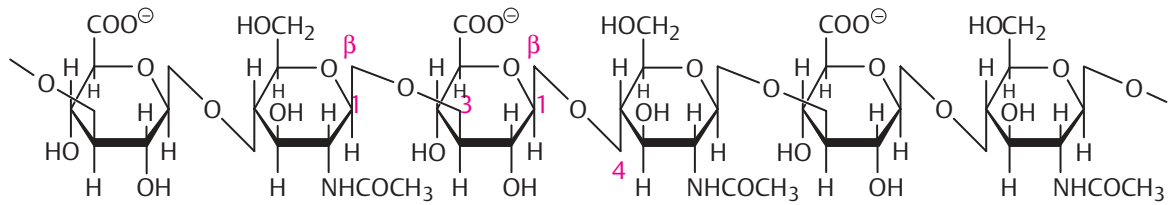
Like all *N*-linked carbohydrates, the oligosaccharide in IgG contains a T-shaped **core structure** consisting of two *N-acetylglucosamines* and three *mannose* residues (shown in violet). In addition, in this case the structure contains two further *N-acetylglucosamine* residues, as well as a *fucose* residue and a *galactose* residue. Glycoproteins show many different types of branching. In this case, we not only have β1→4 linkage, but also β1→2, α1→3, and α1→6 bonds.

### C. Glycoproteins: forms ◑

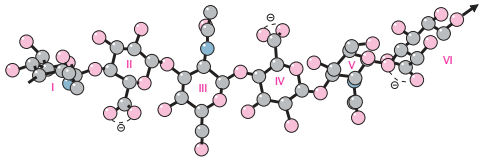
On the cell surface of certain glycoproteins, **O-glycosidic** links are found between the carbohydrate part and a serine or threonine residue, instead of *N*-glycosidic links to asparagine residues. This type of link is less common than the ***N*-glycosidic** one.

There are two types of oligosaccharide structure with *N*-glycosidic links, which arise through two different biosynthetic pathways. During glycosylation in the ER, the protein is initially linked to an oligosaccharide, which in addition to the core structure contains six further mannose residues and three terminal glucose residues (see p. 230). The simpler from of oligosaccharide (the **mannose-rich** type) is produced when only the glucose residues are cleaved from the primary product, and no additional residues are added. In other cases, the mannose residues that are located outside the core structure are also removed and replaced by other sugars. This produces oligosaccharides such as those shown on the right (the **complex type**). At the external end of the structure, glycoproteins of the complex type often contain *N*-acetylneuraminic acid residues, which give the oligosaccharide components negative charges.

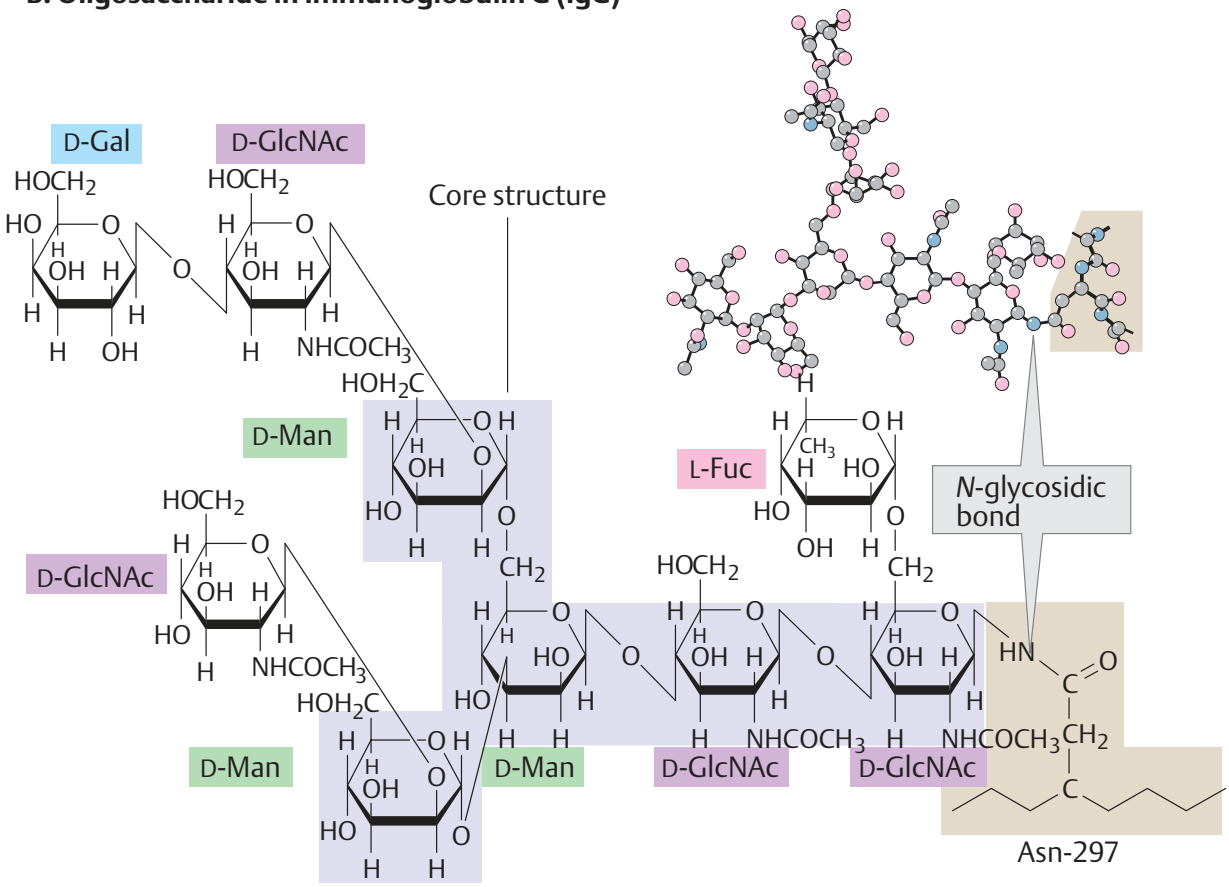
## A. Hyaluronic acid




[→3)-β-D-GlcNAc-(1 →4)-β-D-GlcUA-(1 →4]n



## B. Oligosaccharide in immunoglobulin G (IgG)




## C. Glycoproteins: forms