Biochemistry

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Any suggestions for improvements would be greatly appreciated.

Near the further end a low arched passage branched away from it and led to the chemical laboratory. This was a lofty chamber, lined and littered with countless bottles. Broad, low tables were scattered about, which bristled with retorts, test-tubes, and little Bunsen lamps, with their blue flickering flames. There was only one student in the room, who was bending over a distant table absorbed in his work. At the sound of our steps he glanced round and sprang to his feet with a cry of pleasure. "I've found it! I've found it," he shouted to my companion, running towards us with a test-tube in his hand. "I have found a re-agent which is precipitated by hoemoglobin, and by nothing else." Had he discovered a gold mine, greater delight could not have shone upon his features.

"Dr. Watson, Mr. Sherlock Holmes," said Stamford, introducing us.

–Arthur Conan Doyle, *A Study in Scarlet* (1887)

"It was all done that evening and night. While I was still sitting under the sickly, drowsy influence of the drugs that decolourise blood, there came a repeated knocking at the door... It was my landlord, with a notice of ejectment or something... For a moment he gaped. Then he gave a sort of inarticulate cry, dropped candle and writ together, and went blundering down the dark passage to the stairs... I shall never forget that dawn, and the strange horror of seeing that my hands had become as clouded glass, and watching them grow clearer and thinner as the day went by, until at last I could see the sickly disorder of my room through them, though I closed my transparent eyelids. My limbs became glassy, the bones and arteries faded, vanished, and the little white nerves went last. I gritted my teeth and stayed there to the end. At last only the dead tips of the fingernails remained, pallid and white, and the brown stain of some acid upon my fingers... I went and stared at nothing in my shaving-glass, at nothing save where an attenuated pigment still remained behind the retina of my eyes, fainter than mist. I had to hang on to the table and press my forehead against the glass. It was only by a frantic effort of will that I dragged myself back to the apparatus and completed the process."

–Griffin, in H. G. Wells' *The Invisible Man* (1897)

Overview

Biochemistry covers the chemical molecules and reactions that are important in biology. Most biological molecules fall into five categories: (1) nucleic acids such as deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and their component nucleotides; (2) proteins and their component amino acids; (3) lipids such as fatty acids, triglycerides, and cholesterol; (4) carbohydrates such as simple sugars and various polymers composed of them; and (5) iron- or magnesium-containing porphyrins in hemoglobin, chlorophyll, etc. Most biochemical reactions have many steps, each of which is catalyzed by different enzymes, proteins that act as specialized molecular machines to greatly speed up and control reactions. Some major types of biochemical reactions include the synthesis (production) or catabolism (degradation) of proteins, nucleic acids, lipids, carbohydrates, and porphyrins. Other important biochemical reactions include respiration, in which energy is produced by combining hydrogen from biomolecules with oxygen from the air to form water; fermentation, in which smaller amounts of energy are extracted from biomolecules without oxygen; and photosynthesis, basically respiration run in reverse so that light energy is absorbed and stored by splitting water into more oxygen for the air and more hydrogen in biomolecules.

Contents

1 A Biochemical Beastiary

Biochemistry, the study of chemical molecules and reactions important in biology, is the link between biology and chemistry, and the foundation for all other biology subjects (Fig. 1).

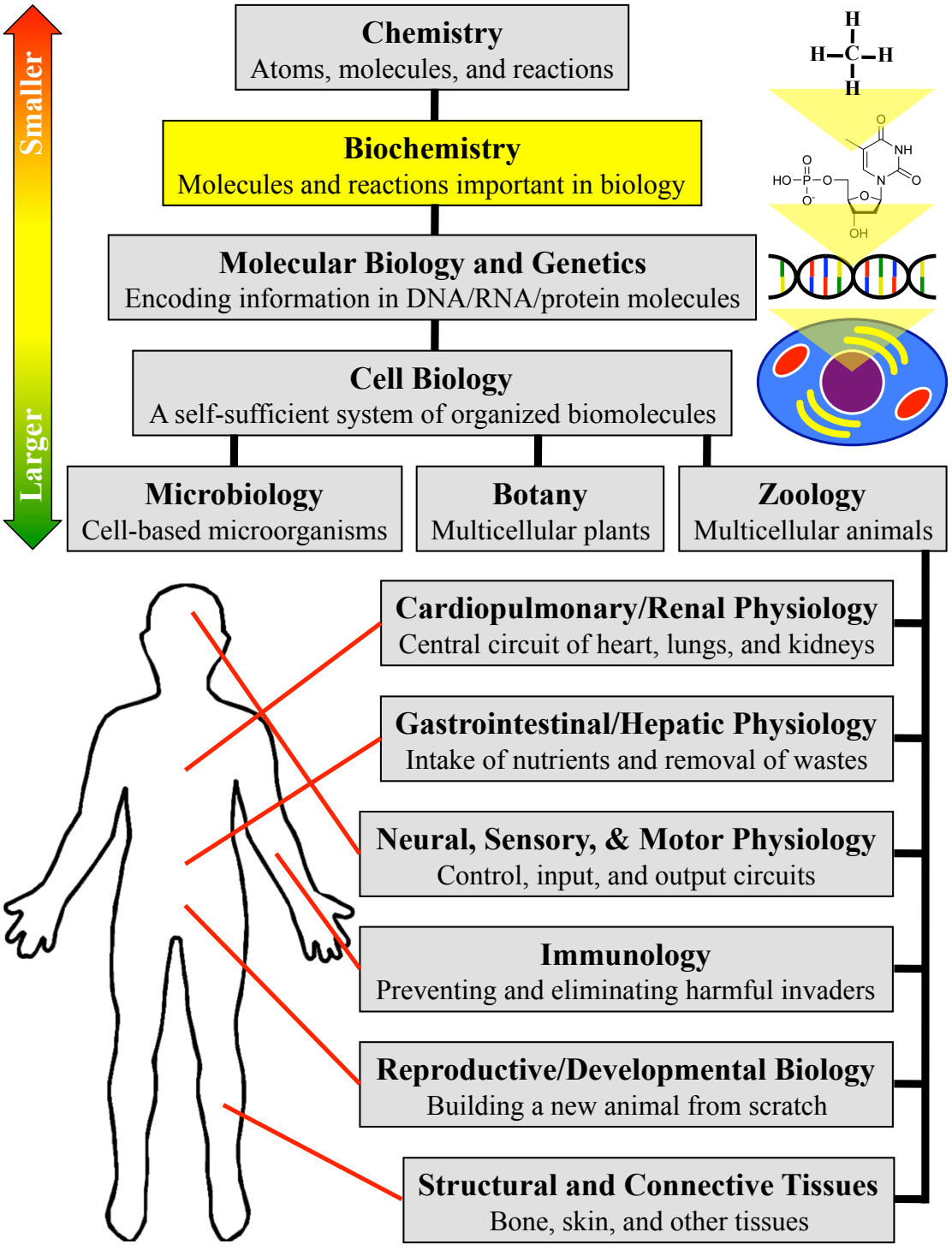


Fig. 1. Relationship between biochemistry and other subjects.

This section will give an overview of the various types of biologically relevant molecules and reactions, then discuss how enzymes play key roles in catalyzing those reactions of biomolecules.

1.1 Categories of Biomolecules

Before we cover the major types of biological molecules, you need a brief crash course in biochemistryese using the handy information presented in Fig. 2.

The flavors of atoms that appear most commonly in biological molecules and reactions are shown in Fig. 2(a):

- **Hydrogen** (H) atoms usually appear as part of a larger biomolecule, with one electron bond from the hydrogen atom (H) to the rest of the molecule; they are probably the most plentiful atoms in biomolecules. They can also appear as individual positively charged hydrogen ions or protons (H^+) floating around in liquid solutions.
- **Chlorine** (Cl) atoms can also have one electron bond to a larger biomolecule (usually not in natural biomolecules, but sometimes in biologically active artificial drug molecules), or they can be individual negatively charged chloride ions (Cl^-) floating around.
- **Fluorine** (F) atoms generally do not appear in natural biomolecules but are sometimes used in biologically active drugs; they form single electron bonds.
- **Oxygen** can appear in biomolecules as oxygen atoms (O) with two electron bonds, or as negatively charged oxygen ions (O^-) with one electron bond.
- **Sulfur** (S) atoms can also appear in biomolecules as atoms with two electron bonds.
- **Nitrogen** can appear as nitrogen atoms (N) with three electron bonds, or as positively charged nitrogen ions (N^+) with four electron bonds.
- **Carbon** (C) almost always appears as carbon atoms with four electron bonds, and are the most important structural components of biomolecules.
- **Phosphorus** (P) appears as atoms with five single electron bonds, or much more often as atoms with three single electron bonds and one double electron bond.
- **Sodium** generally appears as sodium ions (logically spelled Na^+) with a single positive charge floating around in solution.
- **Potassium** likewise usually appears as potassium ions (abbreviated K^+ because of that prominent "K" sound in potassium) that have a single positive charge and that float around.
- **Iron** generally appears as ions (Fe^{2+} or sometimes Fe^{3+} just be even more confusing) with two or three positive charges, either floating around or closely associated with a biomolecule like heme.
- **Magnesium** generally appears as ions (Mg^{2+}, wow, like the name!) with two positive charges, either floating around or closely associated with a biomolecule like chlorophyll.
- **Zinc** also appears as ions (Zn^{2+}) with two positive charges, either floating around or closely associated with a biomolecule such as a protein.
- **Calcium** usually appears as ions (Ca^{2+}) with two positive charges, either floating around or closely associated with a biomolecule such as a protein.

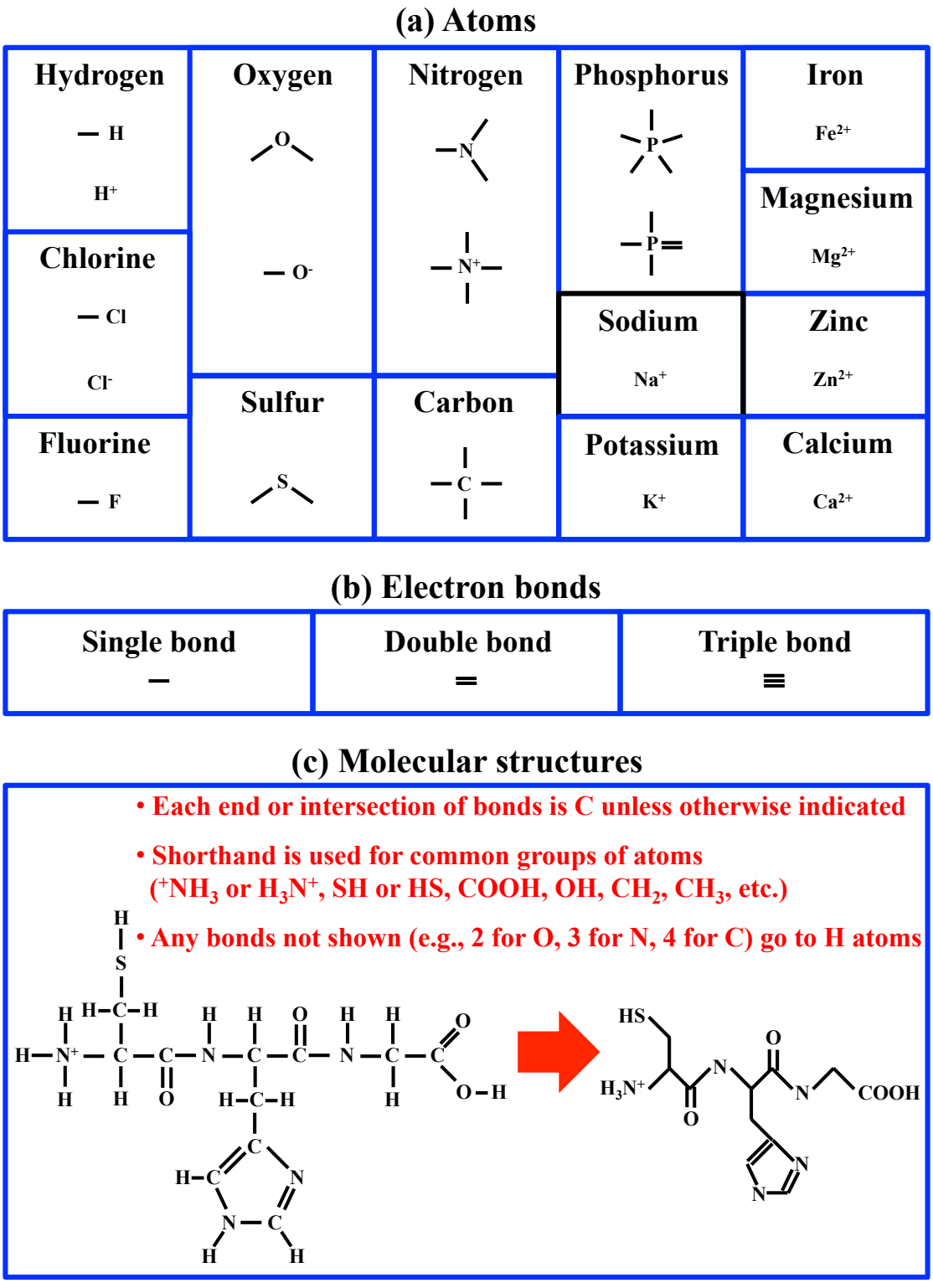


Fig. 2. Biochemistry notation for (a) atoms, (b) electron bonds, and (c) molecular structures.

Electron bonds connect one atom to another atom in molecules. Each electron bond contains a pair of electrons, generally one electron from one atom and the other electron from the other atom, but they are married so they share nicely. Like fast food meals, electron bonds may be ordered in three sizes, as illustrated in Fig. 2(b):

- **Single bonds** just involve a pair of electrons and are the most common type.

- **Double bonds** involve two pairs of electrons and use up two of the available bonds from each atom to which they are connected. Most commonly they connect an oxygen to a carbon (O=C), although they can occur between other atoms as well (C=C, C=N, etc.).

- **Triple bonds** involve three pairs of electrons, use up three of the available bonds from each atom to which they are connected, and are relatively rare in biological molecules.

If two atoms are connected by a single bond, one atom is free to rotate relative to the other. In contrast, atoms that are connected by double or triple bonds cannot rotate and have to just live with that.

The structures of biological molecules tend to be very complicated, and biologists tend to be very lazy. Thus in drawing biomolecules, biologists often make some or all of the following simplifications, as illustrated in the example in Fig. 2(c):

- Each end or intersection of bonds (anyplace that lines cross or bend) is a carbon atom (C) unless otherwise indicated.

- Shorthand is used for common groups of atoms without explicitly showing the bonds between them (for example, $^{+}NH_3$ or H_3N^{+}, SH or HS, COOH, OH, CH_2, CH_3, etc.).

- Any bonds not shown (2 for O or S, 3 for N, 4 for N^{+} or C, etc.) go to hydrogen (H) atoms. That makes it very important to remember the numbers of bonds that each atom should have, as shown in Fig. 2(a). Then keep in mind that all of those missing bonds that are not shown in biochemistry illustrations are really there and are connected to invisible hydrogen atoms, even if the nefarious biochemists have not explicitly shown that.

The electron bonds from each atom like to be as far apart (in angles) as possible. We will shamelessly smush biomolecules into two-dimensional figures, but always bear in mind that each atom's bonds are generally spread out in three dimensions and that each biomolecule is actually a three-dimensional beastie.

Okay, if you are still awake, now we are finally ready for some actual biochemistry. As illustrated in Fig. 3, there are five major categories of biomolecules:

1. Nucleic acids include deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), and are used to store and transmit genetic information. They are composed of individual nucleotides strung together. Fig. 3 shows four nucleotides of DNA, containing adenine, cytosine, guanine, and thymine. RNA is extremely similar, except each blue hydrogen (H) in DNA is a hydroxyl (OH) in RNA, and the red methyl (CH_3) in thymine in DNA is just a hydrogen (H) in uracil in RNA. In addition to being strung together to make genes, two nucleotides (adenine- and guanine-containing nucleotides) play key roles individually. Adenosine triphosphate (ATP) and guanosine triphosphate (GTP) are very important sources of energy that power most things in cells. Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are frequently used to send signals inside cells.

2. Proteins are commonly thought of as meat or muscle. As shown in Fig. 3, each protein is composed of different amino acids strung together. Depending on the specific amino acids, the red Rs in Fig. 3 could stand for anything from a simple hydrogen (H) to a whole ring of interconnected atoms. Individual proteins do most of the important jobs in cells, from serving as structural building blocks to acting as little nanomachines to carry out specialized jobs.

3. Lipids are the fatty greasy stuff that you think you aren't supposed to eat, but everyone needs at least some of them. They include fatty acids, triglycerides, cholesterol, and other molecules. They all contain a lot of carbons (C) and hydrogens (H) and not much else, so they don't have much electrical charge or electrical polarity, whereas water molecules (H_2O) are very polar (fairly negative oxygen and fairly positive hydrogens). As a result, lipids are hydrophobic–they don't like to be in water. Thus lipids will float on the top of water, form clumps in water, or do anything but dissolve in water. That's why you have to use soap (another lipid) to get greasy residue off dinner plates, instead of simply rinsing them with water.

4. Carbohydrates are mainly composed of carbon (C), hydrogen (H), and oxygen (O). The most familiar carbohydrates are sugars, including simple or blood sugar (glucose, shown in Fig. 3), fruit sugar (fructose), table sugar (sucrose), milk sugar (lactose), etc. Individual sugars can be strung together in various ways to make everything from starch to cell walls to that super coating that makes cockroaches so darned indestructible.

5. Porphyrins are flower-shaped molecules with a metal ion [usually iron (Fe) or magnesium (Mg)] at their center. They generally help to convert one form of energy into another, doing everything from transporting oxygen in the blood (hemoglobin) to absorbing light in plants (chlorophyll).

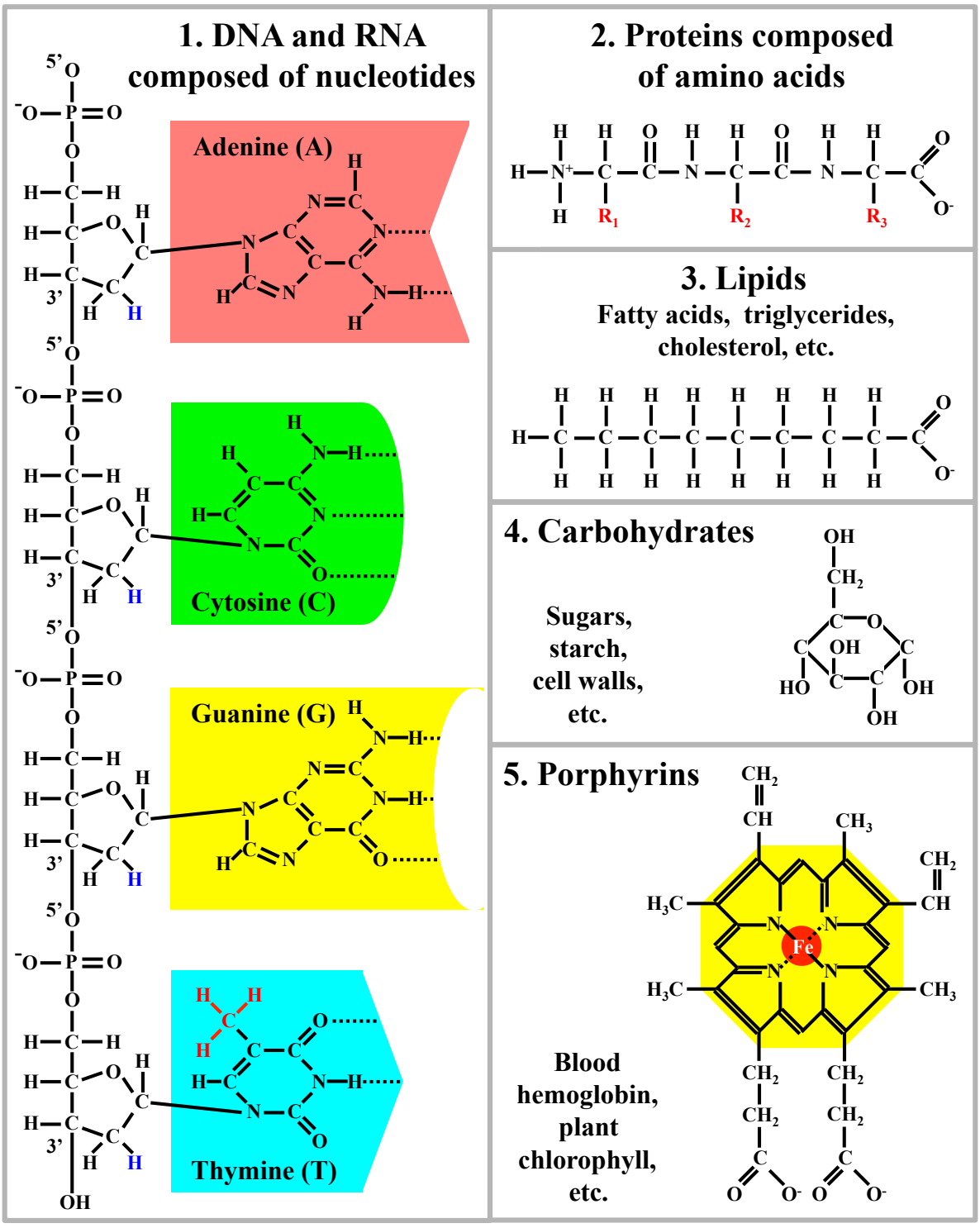


Fig. 3. Most biological molecules fall into five categories: (1) nucleic acids such as deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and their component nucleotides; (2) proteins and their component amino acids; (3) lipids such as fatty acids, triglycerides, and cholesterol; (4) carbohydrates such as simple sugars and various polymers composed of them; and (5) iron- or magnesium-containing porphyrins in hemoglobin, chlorophyll, etc.

Now you are about to be plunged up to your neck in biochemistry, but please take a deep breath and try not to panic. Figure 4 shows an overview of major biochemical pathways. Most reactions involving biomolecules have many steps, each of which is facilitated by different **enzymes (Section 1.2)**, proteins that act as specialized catalysts to greatly speed up and control reactions.

Important pathways include:

1. **Synthesis** (production) or **catabolism** (degradation) of biomolecules including:
   - **Nucleotides for DNA and RNA (Section 2).** As needed, new nucleotides are built by combining monosaccharides (simple sugars) and amino acids. Old nucleotides are either recycled to form new stretches of DNA and RNA, or degraded to form uric acid and other waste products.
   - **Amino acids for proteins (Section 3).** Amino acids may be derived by breaking apart old proteins (or proteins that an animal has eaten) into their component amino acids, or by building them from scratch using parts and pieces kidnapped from the sugar-consumption pathways (glycolysis and citric acid cycle). Unwanted amino acids are broken down to form urea, from which urine gets its name (and smell!).
   - **Lipids such as fatty acids, triglycerides, phospholipids, cholesterol, etc. (Section 4).** Lipids may be derived from consumed food or built from scratch (lipogenesis). Excess lipids may be stored (as many of us do!), dismantled and reformed into new lipids, or used as fuel for the respiratory pathway to power the cell.
   - **Carbohydrates (Section 5).** Individual simple sugars can be strung together in various ways to make complex carbohydrates ranging from starch to glycogen to cell walls, or those complex carbohydrates can be split apart into their component simple sugars. Simple sugars make great fuel for the respiratory pathway.
   - **Porphyrins (Section 6).** These frequently overlooked biomolecules are key catalytic components of a number of energy conversion pathways including respiration and photosynthesis. They contain iron or magnesium metal ions and turn lots of different colors like mood rings, from green in plant chlorophyll to red in oxygen-rich blood hemoglobin to blue in oxygen-deprived hemoglobin. Porphyrins are very complicated flower-shaped molecules that cells build from scratch. Old porphyrins are broken down to form bilirubin, a toxic waste product that makes urine yellow and poop brown. Too much information!
2. **Respiration (Section 8)**, in which energy is produced by combining hydrogen extracted from biomolecules with oxygen from the air to form water. Respiration occurs in organelles called mitochondria in animal, plant, and fungal cells, or in similar structures in bacterial cells.
3. **Fermentation (Section 9)** is an alternative process that produces a much smaller amount of energy than respiration (by converting sugars to lactic acid and/or ethyl alcohol) but is used by many organisms if oxygen is not available (for example in anaerobic bacteria or yeast growing without fresh air).
4. **Photosynthesis (Section 10)** in plant cells is basically respiration in reverse; light energy is absorbed and stored by splitting water into more oxygen for the air and more hydrogen in biomolecules. Photosynthesis occurs in organelles called chloroplasts in plant and algae cells, or in similar structures in photosynthetic bacteria.

These biochemical pathways will be covered in nauseating detail in the course of this summary.

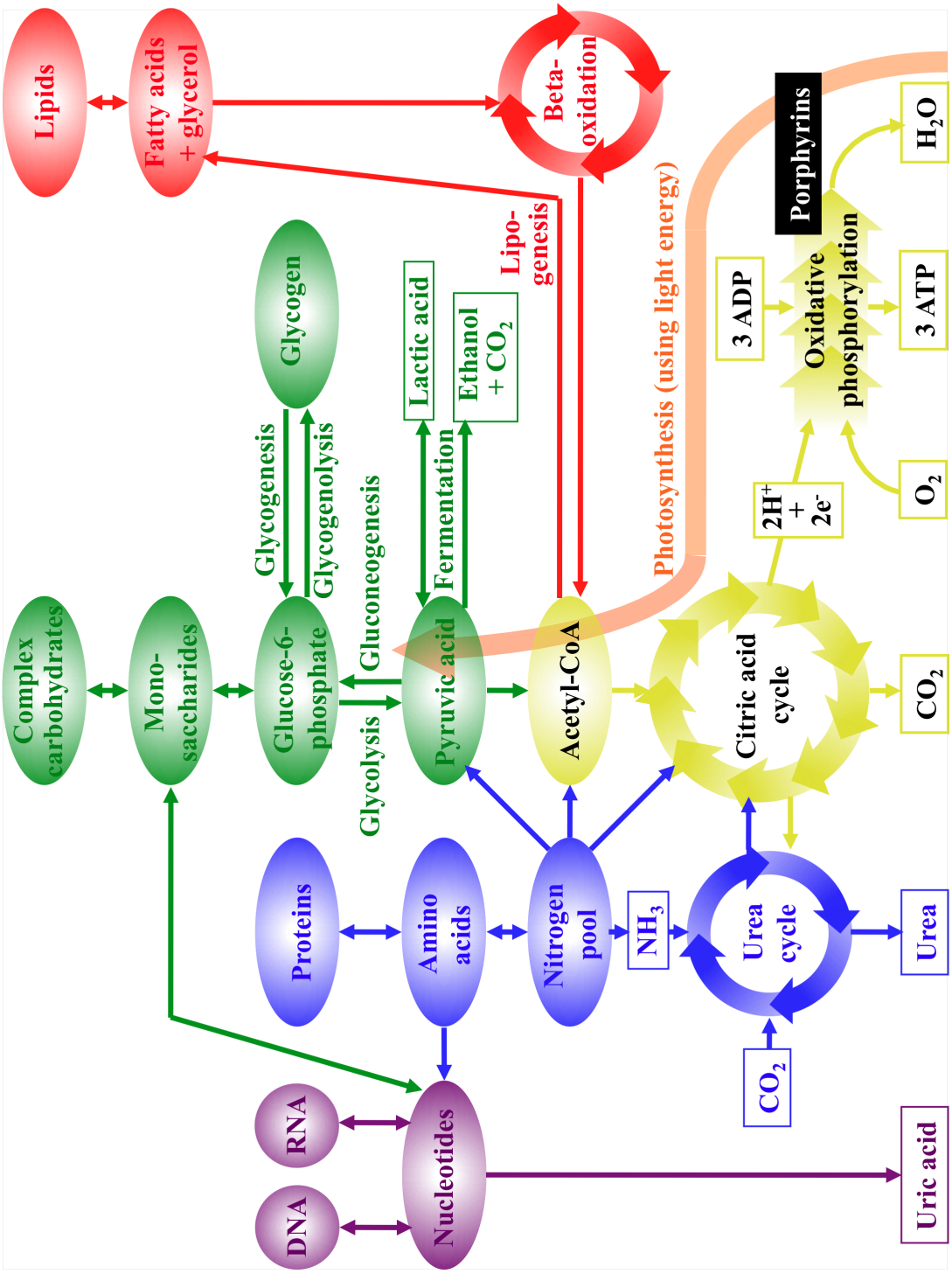


Fig. 4. Major biochemical pathways include: (1) synthesis (production) or catabolism (degradation) of nucleic acids, proteins, lipids, carbohydrates, and porphyrins; (2) respiration, in which energy is produced by combining hydrogen from biomolecules with oxygen from the air to form water; and (3) photosynthesis (in plant cells), the reverse process in which light energy is absorbed and stored by splitting water into more oxygen for the air and more hydrogen in biomolecules. Porphyrins play catalytic roles in respiratory/photosynthetic pathways.

1.2 Enzymes

If you have made it this far, you now know that biological systems like us depend upon many different biochemical pathways, and that each of those pathways has many different steps of necessary chemical reactions among its various molecules, making (in nice round numbers) about a zillion different essential biochemical reactions. If those reactions were left to proceed on their own, they might take thousands of years, or the wrong molecules might react with each other.

That's why biology invented enzymes. Enzymes are proteins that are specialized at guiding and facilitating or catalyzing different biochemical reactions. There is a different enzyme for virtually every different type of biochemical reaction, or nearly a zillion different enzymes, so studying them has provided gainful employment for generations of biology nerds who would otherwise have starved while watching Star Trek reruns. Each enzyme is very skilled at carrying out its own specific type of reaction and does nothing else. Actually most of the biology nerds are like that too.

Figure 5(a) shows the structure of a typical enzyme. The enzyme has a **binding site** with a shape that corresponds to the shape of the specific molecule(s) (called the **substrate**) on which the enzyme is supposed to act. Somewhere inside the binding site is the **catalytic site**, the part of the enzyme that actually catalyzes or facilitates the desired chemical reaction.

The effect of an enzyme on a reaction is illustrated in Fig. 5(b). Initial molecule(s) undergo a chemical reaction to become final molecule(s); in this illustration, a long red substrate molecule splits into two parts. The graph shows the energy required for each step. Although the reaction releases net energy (the final products have less stored energy than the initial products), getting through the reaction involves getting over an energy hump. Think of the energy hump as going to bed. You may be tired in the evening, but you still have to temporarily put in extra energy to brush your teeth and get ready for bed before you can go to sleep. It may seem difficult to muster the extra energy at the time, but in the end you're glad you did it and you get to fall asleep in an even lower and more comfortable energy state. Just as kids left on their own may not find the temporary energy required to brush their teeth, molecules left on their own may not find the temporary energy required to undergo a chemical reaction. Like parents, enzymes help by lowering the required energy, guiding and expediting the process to ensure that all the molecules get their teeth brushed and all the kids have a reaction.

I know you signed up for biology instead of physics because math is scary, but in order to analyze enzymes in more detail, we're going to do a small amount of math. Just take comfort in the fact that this isn't physics, or we would be doing math for the next 80 pages. The initial reaction rate or velocity when enzymes and substrates are first mixed together is V_0, and the maximum possible reaction rate is $V_{\max}$. The substrate concentration is $[S]$. How fond the enzyme is for the substrate is called the binding constant K_M. If the enzyme is so eager to work that it will pounce on even low concentrations of substrate to catalyze reactions, K_M is low. On the other hand, if the enzyme is a lazy procrastinator and cannot be bothered to bind to substrates until its "in box" is piled high with a backlog of substrates to work on (the substrate concentration is high), K_M is high. $[S]$ and K_M are measured in the same units, usually micromolar (μM or millionths of a molar) or millimolar (mM or thousandths of a molar), where 1 molar (M) = 1 mole/liter $\approx 6.022 \times 10^{23}$ molecules/liter, just as you had to suffer through in chemistry. V_0 and $V_{\max}$ are measured in the same units as each other, usually μM/second.

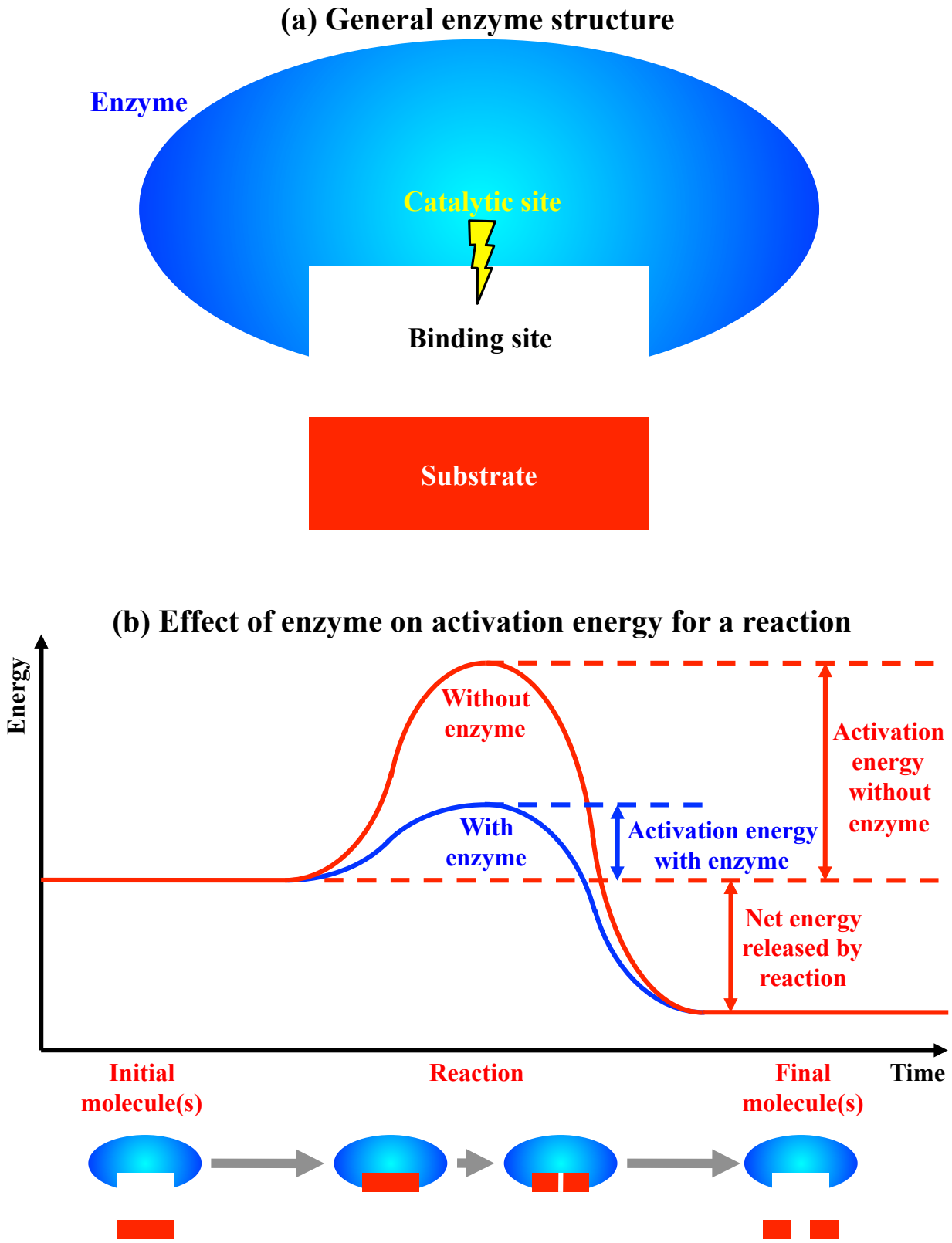


Fig. 5. Enzymes (a) bind to a substrate and (b) decrease the activation energy required for the substrate to undergo a particular chemical reaction.

To be more precise, the binding constant K_M is the substrate concentration required for half the enzymes to be busy doing their thing with substrate molecules, or for the initial reaction velocity to be half the maximum reaction velocity that would be possible if all of the enzymes were hard at work in their cubicles:

$$[S] \;=\; K_M \;\;\Longrightarrow\;\; V_0 \;=\; \frac{V_{\max}}{2} \tag{1}$$

At very low substrate concentrations $[S]$, the initial reaction velocity is proportional to $[S]$ (there are plenty of enzymes but very few substrate molecules, so doubling the amount of substrate doubles the amount of reactions):

$$[S] \;\ll\; K_M \;\;\Longrightarrow\;\; V_0 \;\propto\; [S] \tag{2}$$

At very high substrate concentrations $[S]$, the initial reaction velocity approaches its maximum possible value $V_{\max}$ (increasing the substrate concentration further doesn't do any good, because all of the enzymes are already busy working on substrates):

$$[S] \;\gg\; K_M \;\;\Longrightarrow\;\; V_0 \;\approx\; V_{\max} \tag{3}$$

A more general equation that gives the results from Eqs. (1)-(3) for those substrate concentrations is the **Michaelis-Menten equation**, as graphed in Fig. 6(a):

$$V_0 \;\;=\;\; \frac{V_{\max}\,[S]}{K_M + [S]} \tag{4}$$

Note that at very low substrate concentrations $[S]$ in Eq. (4), the initial reaction velocity increases linearly with the substrate concentration, as predicted by Eq. (2):

$$[S] \;\ll\; K_M \;\;\Longrightarrow\;\; V_0 \;\approx\; \frac{V_{\max}}{K_M}\,[S] \tag{5}$$

As graphed in Fig. 6(a), the Michaelis-Menten equation (4) is a curve. It is fairly hard to accurately plot a curve (where does it curve, by how much, etc.?), but much easier to plot a straight line (all you need is a ruler). Therefore, as weird as this seems, it is much easier to graph the inverse of the initial reaction velocity $(1/V_0)$ versus the inverse of the substrate concentration $(1/[S])$. That turns out to be a straight line, called the **Lineweaver-Burk equation** and graphed in Fig. 6(b):

$$\frac{1}{V_0} \;\;=\;\; \frac{1}{V_{\max}} \;+\; \frac{K_M}{V_{\max}}\,\frac{1}{[S]} \tag{6}$$

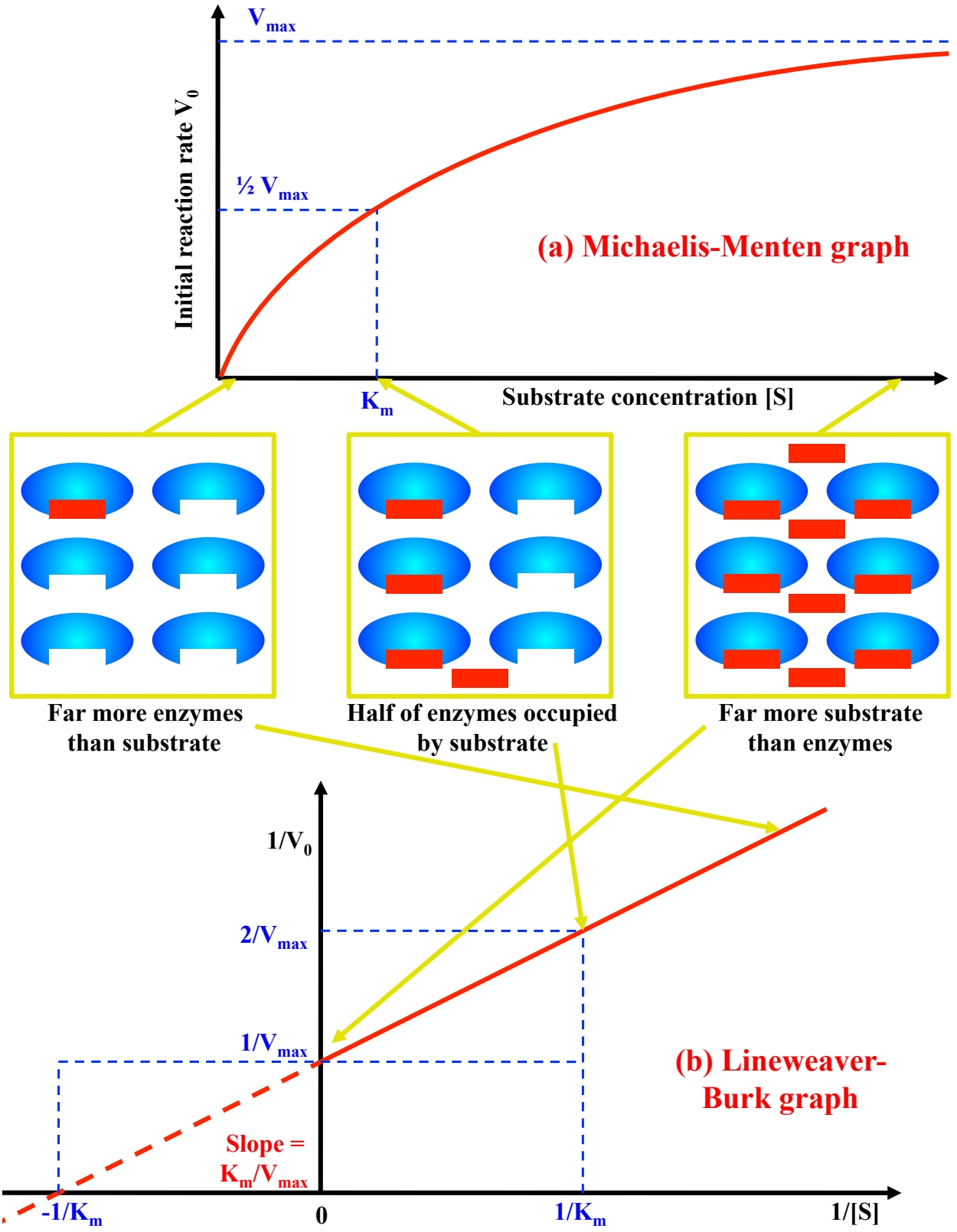


Fig. 6. Initial reaction rate V_0 vs. substrate concentration [S] is a curve on a Michaelis-Menten graph, but $1/V_0$ vs. $1/[S]$ is a straight line on a Lineweaver-Burk graph.

Some diseases are caused by certain enzymes running amok, so many therapeutic drugs are chemical molecules that selectively inhibit or block those particular enzymes. Most enzyme inhibitors fall into two categories:

- **Competitive inhibitors** are chemical molecules that enzymes can mistakenly grab instead of their proper substrates, as shown in Fig. 7(a). Think of competitive inhibitors as cans of Diet Coke that science nerds (acting like enzymes) mistakenly grab when what they really want is their proper substrates, cans of real Coke. At very high concentrations of the proper substrate $[S]$, the proper substrates drown out the inhibitors and find their rightful places with the enzymes, so the maximum reaction velocity $V_{\max}$ does not change. However, at lower substrate concentrations, some enzymes grab an inhibitor molecule and some enzymes grab the right substrate. That increases the effective binding constant K_M, making it seem as if the enzymes are less eager to grab and work on their proper substrates.

- **Noncompetitive inhibitors** are chemical molecules that do not simply get mistaken for substrates, but rather bind to and shut down enzymes in other ways, as shown in Fig. 7(b). Think of noncompetitive inhibitors as putting the science nerds (enzymes) to sleep so they don't realize just how caffeine-deprived they are without their normal Coke substrates. Noncompetitive inhibitors do not modify the effective binding constant K_M, but rather they permanently take some enzymes out of commission, effectively lowering the maximum reaction velocity $V_{\max}$. In practice, most noncompetitive inhibitors bind somewhere on the back of the enzyme and cause the enzyme to change shape so that it can no longer bind to its intended substrate. [They usually don't form a giant shield as in Fig. 7(b); we were just being cute to illustrate the general idea.]

Enzymes are proteins, long chains of amino acids all folded up in the right way to act as little machines to catalyze specific reactions. Under sufficiently harsh conditions, enzymes **denature** or unfold and are no longer able to do their job. Often even if the conditions become right again, denatured enzymes do not renature or refold correctly, just as an unfolded origami animal usually doesn't spontaneously refold itself. (Or if your origami animals do spontaneously refold themselves, you could have a much more lucrative career than biochemistry.)

Figure 8(a) shows the effect of temperature changes on enzymes. Enzymes in organisms have been naturally optimized to work best at the normal temperatures of those organisms, denoted as T_0 on the graph. Most enzymes in humans work best around normal human body temperature of 37^oC or so. Enzymes in plants or coldblooded animals may work best at lower environmental temperatures. Enzymes in bacteria that live in hot springs or deep sea thermal vents work best at temperatures far higher than 37^oC. At temperatures lower than T_0, enzyme activity falls off rapidly since there is insufficient thermal energy to aid the enzymatic reaction. At temperatures lower than T_0, enzyme activity falls off rapidly since the excessive thermal energy causes the enzyme to denature. This is fairly similar to how people operate; you probably do your best work when you are at some comfortable temperature, but at lower temperatures you are too busy shivering to work, and at higher temperatures you are too busy sweating.

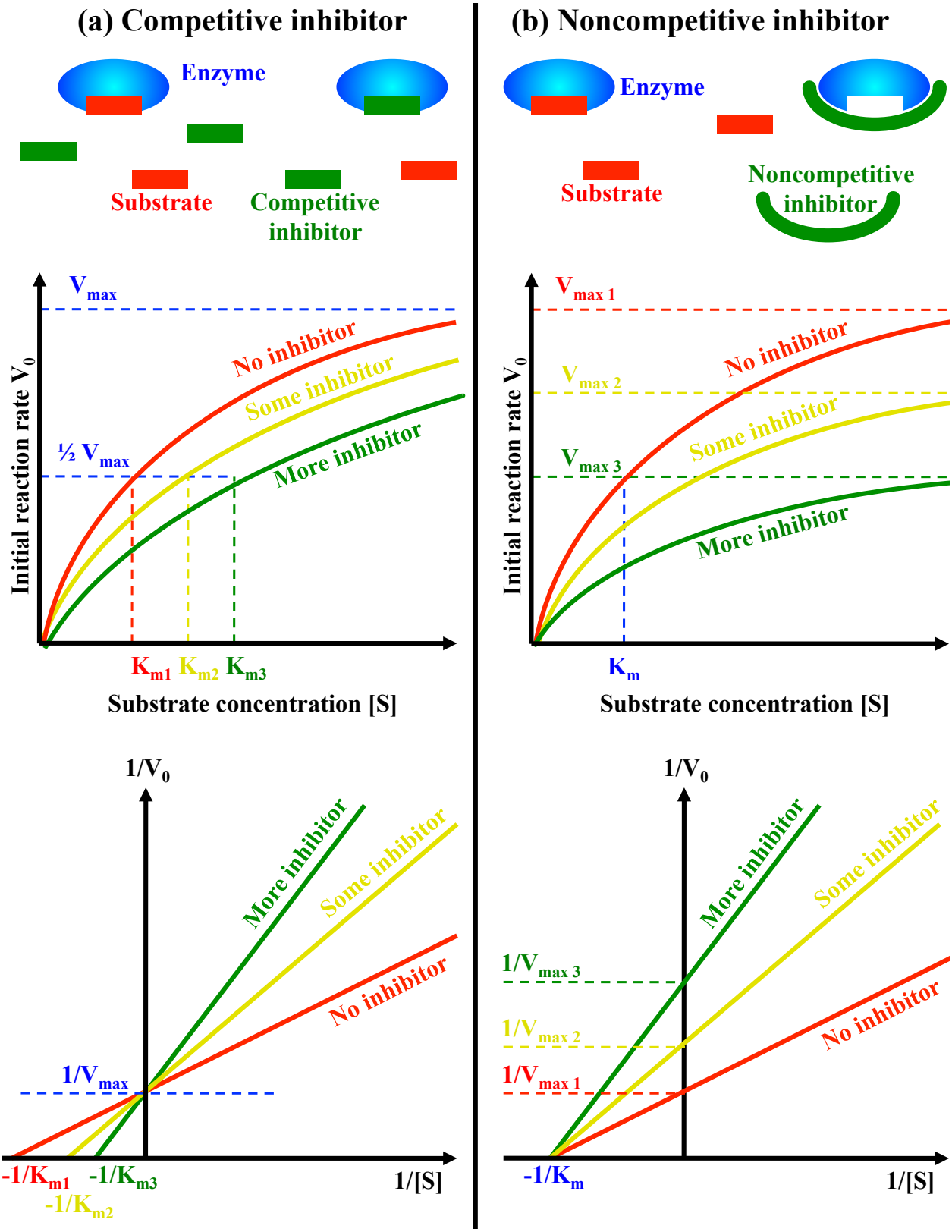


Fig. 7. Enzyme inhibitors may be (a) competitive or (b) noncompetitive.

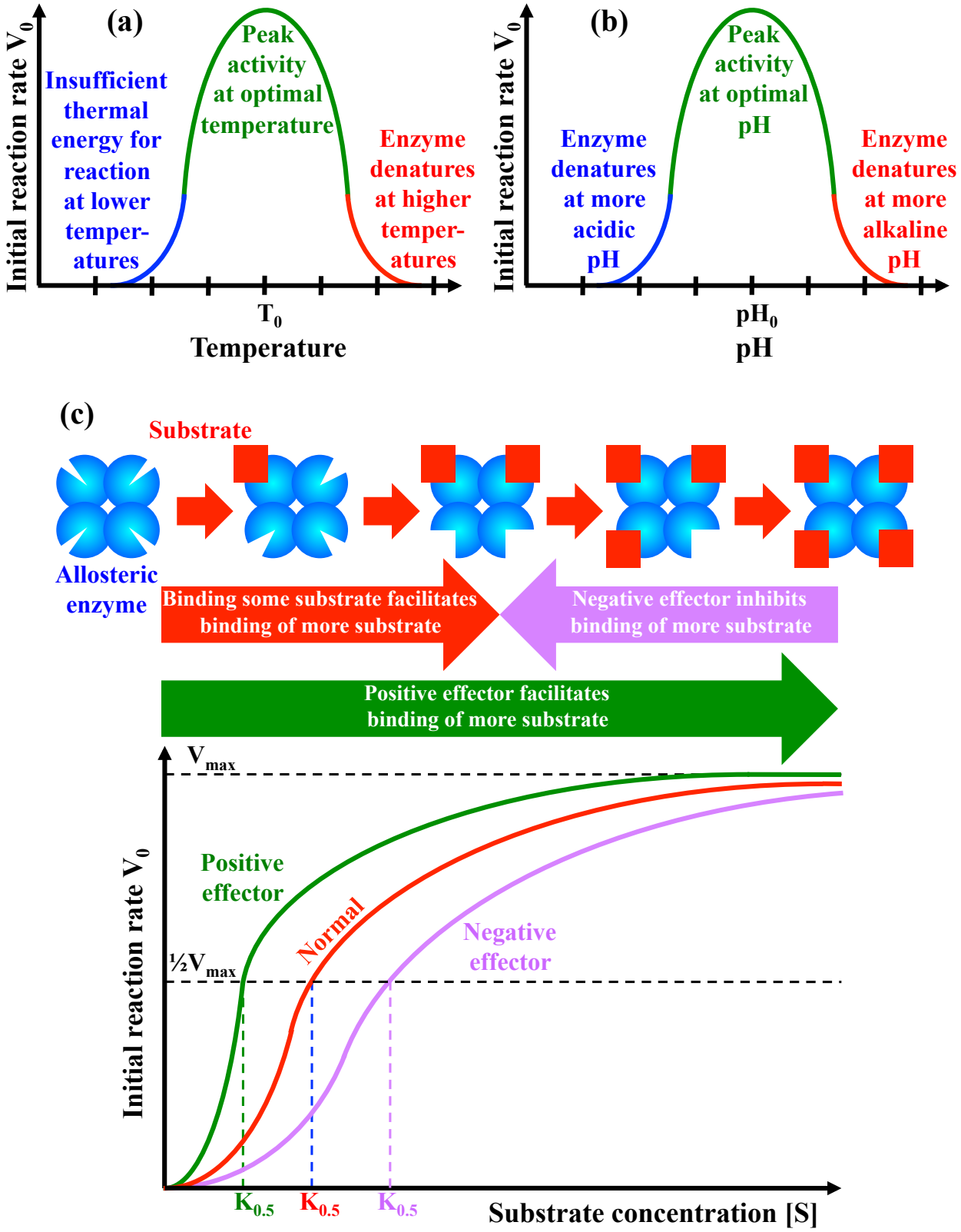


Fig. 8. Effects on enzymes of (a) temperature changes, (b) pH changes, and (c) allosteric or cooperative binding of multiple substrates to each enzyme.

Similarly, Fig. 8(b) shows the effect of pH (acidic vs. neutral vs. alkaline solution) changes on enzymes. Enzymes have been naturally optimized to work best at the pH they are normally exposed to, denoted as pH_0 on the graph. Many enzymes work best around a neutral pH of 7, but those intended to operate in acidic parts of cells or organisms work best at lower pH values, and those intended to operate in alkaline parts of cells or organisms work best at higher pH values. At pH values lower than pH_0, enzyme activity falls off rapidly since the acidic conditions cause the enzyme to denature. Enzyme activity also falls off rapidly at pH values higher than pH_0 since the alkaline conditions cause the enzyme to denature.

Although most enzymes obey the Michaelis-Menten Eq. (4) as graphed in Fig. 6(a), some weirdo enzymes do not. Those enzymes are generally **allosteric**, or have cooperative binding of multiple substrates to the same enzyme, as illustrated in Fig. 8(c):

- Binding of one or more substrate molecules to an allosteric enzyme facilitates binding of more substrate molecules to the same enzyme [red arrow and curve in Fig. 8(c)]. Think of allosteric enzymes as science nerds who are so sleepy in the morning that they have trouble grabbing their first can of Coke, but then they are more awake and grab the second one more quickly, and the third even more quickly, and by the fourth can they are chugging the Cokes and can't sit still. At high substrate concentration $[S]$, the initial reaction rate V_0 still approaches some maximum value $V_{\max}$ just as for a well-behaved Michaelis-Menten enzyme; all enzyme binding sites are already in use, so adding more substrate cannot increase the reaction rate beyond $V_{\max}$. However, at very low substrate concentrations $[S]$, the reaction rate gets off to a much slower start than for a Michaelis-Menten enzyme. For these allosteric enzymes, the substrate concentration for which the reaction rate is half of its maximum value ($V_0 = V_{\max}/2$) is renamed from K_M to $K_{0.5}$ so that Michaelis and Menten won't sue for copyright infringement for using an M in the subscript.

- If a negative effector molecule binds to an allosteric enzyme, it makes it harder than normal for substrate molecules to bind to that enzyme [purple arrow and curve in Fig. 8(c)]. It's like keeping the science nerds up all night for a Star Trek marathon, which will make them more sluggish than normal the next morning no matter how many cans of Coke there are. Negative effector molecules generally bind to and change the shape of allosteric enzymes to make it harder for their active substrate binding sites to open up.

- If a positive effector molecule binds to an allosteric enzyme, it makes it easier than normal for substrate molecules to bind to that enzyme [green arrow and curve in Fig. 8(c)]. Think of positive effectors as like injecting the science nerds with caffeine before they wake up, so they grab even their first can of Coke more quickly than normal. Positive effector molecules generally bind to and change the shape of allosteric enzymes to make their substrate binding sites open for business even if they haven't grabbed their first substrate yet.

2 Nucleic Acids: DNA and RNA

This section will cover the basic biochemistry of nucleic acids, including individual nucleotides, modified nucleotides used for creative purposes in cells, deoxyribonucleic acid (DNA) strands of nucleotides, and ribonucleic acid (RNA) strands of nucleotides. Some of this information may seem rather esoteric, but please do pay attention–when you start working to create a giant mutant pet hamster, you really don't want to mess up.

2.1 Nucleotides

Strands of DNA and RNA are composed of individual nucleotides. Figure 8 shows the structures of DNA and RNA nucleotides. The key distinguishing parts of nucleotides are called bases, because they are chemically basic (proton acceptors) instead of acidic (proton donors), or maybe just because they look like they belong on a baseball diamond. In this and future diagrams, single solid lines represent electron bonds between atoms, double solid lines represent double bonds, and dotted lines represent weak hydrogen bonds (the tendency of certain atoms to snuggle up next to each other).

Apart from a few critical differences, **adenine (A)** and **guanine (G)** look fairly similar to each other (with coupled five-atom and six-atom rings), and they are called **purine** bases [Fig. 9(a)]. Likewise, **cytosine (C)**, **thymine (T)**, and **uracil (U)** look fairly similar to each other with their fashionable six-atom rings, and they are called **pyrimidine** bases [Fig. 9(b)]. Thymine is found only in DNA, and uracil is found only in RNA, so DNA has four possible bases and RNA has four possible bases.

To make a complete nucleotide, you have to glue the base of your choice to ribose, a sugar with a five-atom ring. If the ribose has a hydrogen dangling off the lower right (in blue), it is a DNA (deoxyribose) nucleotide [Fig. 9(c)]. If the ribose has a hydroxyl (OH) dangling off the lower right (in blue), it is an RNA (ribose) nucleotide [Fig. 9(d)]. That may seem like a minute difference in structure, but it makes a large difference in properties. A hydroxyl (OH) is two-thirds of a complete water molecule (H_2O) and really wants to acquire an extra hydrogen, become a normal water molecule, and run away to join the circus. That chemically destabilizes the structure of RNA when it happens, so RNA naturally degrades much more rapidly than DNA. Think of DNA strands as genetic blueprints copied on high-quality, acid-free, archival bond paper, and RNA strands as genetic blueprints copied on cheap newsprint that quickly yellows, crumbles with age, and leaves black stains on your elbows. (Now I hear all of you young folks asking "What is a newspaper?")

Nucleotides may have anywhere from zero to three phosphates attached, where a phosphate is a phosphorous atom (P) surrounded by oxygen atoms (O). A base glued to a ribose is a **nucleoside** if there are no attached phosphates and a **nucleotide** if there are any attached phosphates. A nucleotide with one phosphate is a **monophosphate**, with two is a **diphosphate**, with three is a **triphosphate**, and with four is an overachiever. The naming gets even more (and unnecessarily) complicated when it comes to the different bases and their nucleoside/nucleotide versions, as listed in Tables 1–2. However, obsessing over the details of Tables 1–2 would make biology more painful than conjugating French verbs, so if in doubt, just call the bases/nucleosides/nucleotides/whatever by their first letters: A, C, G, T, and U.

One last point about Fig. 9 is that nucleotides have a polarity. The "upstream" end that gets the phosphates is called the 5' end, and the "downstream" end that has a hydroxyl (OH) for both DNA and RNA is called the 3' end. As we will see in Sections 2.3 and 2.4, when nucleotides are connected together to make strands of DNA or RNA, the 3' end of one nucleotide connects to the 5' end of the next nucleotide, and the sequence of nucleotides (the first letters of their bases) is read in the 5'-to-3' direction.

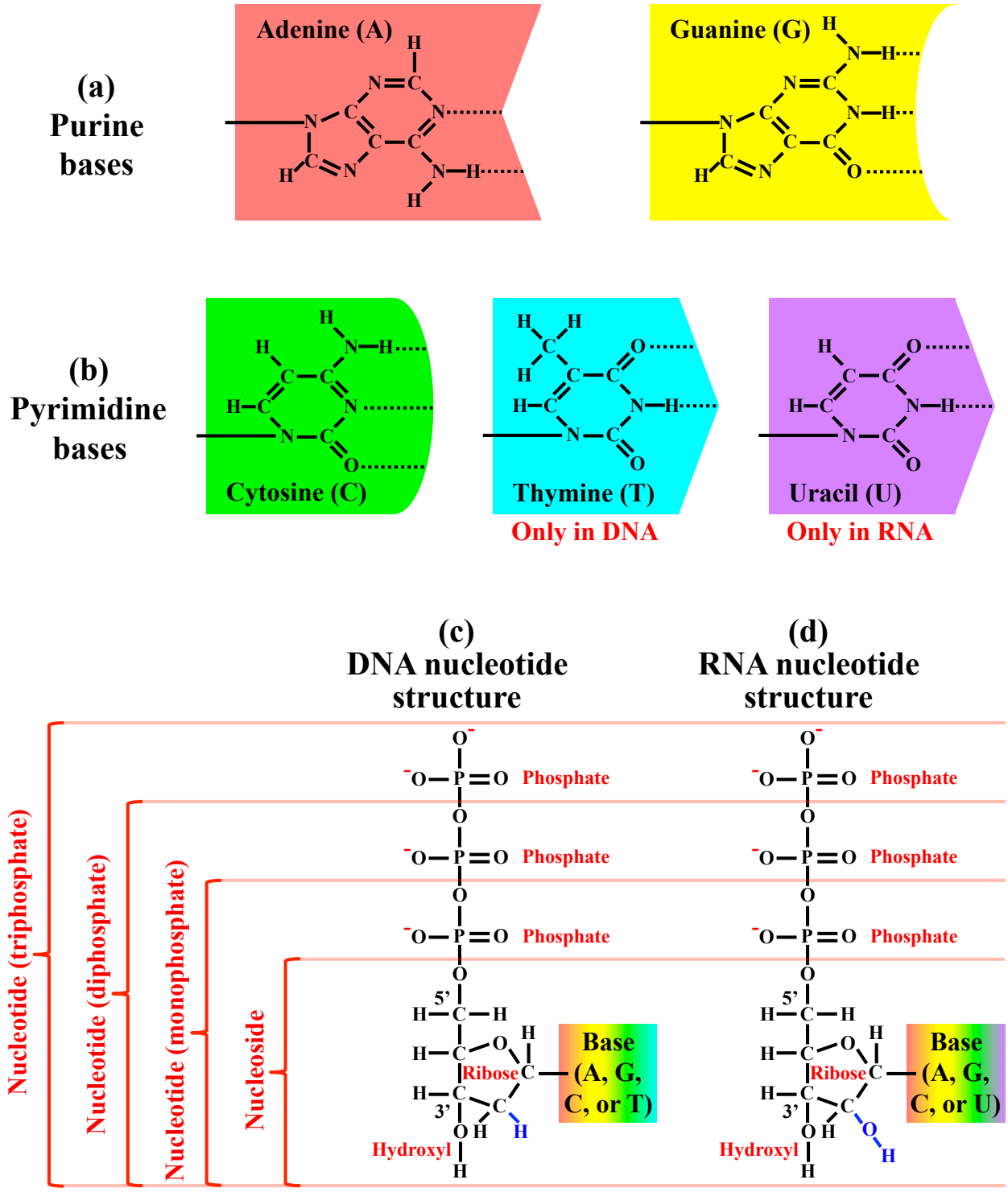


Fig. 9. Structures of DNA and RNA nucleotides: **(a)** purine bases (adenine and guanine), **(b)** pyrimidine bases (cytosine, thymine, and uracil), **(c)** DNA nucleotides with anywhere from 0 to 3 phosphates, and **(d)** RNA nucleotides with anywhere from 0 to 3 phosphates.

Base	Ribonucleoside	Ribonucleotide monophosphate
Adenine (A)	Adenosine	Adenylate monophosphate (AMP)
Cytosine (C)	Cytidine	Cytidylate monophosphate (CMP)
Guanine (G)	Guanosine	Guanylate monophosphate (GMP)
Uracil (U)	Uridine	Uridylate monophosphate (UMP)

Table 1. Names of RNA bases, nucleosides, and nucleotides.

Base	Deoxyribonucleoside	Deoxyribonucleotide monophosphate
Adenine (A)	Deoxyadenosine	Deoxyadenylate monophosphate (dAMP)
Cytosine (C)	Deoxycytidine	Deoxycytidylate monophosphate (dCMP)
Guanine (G)	Deoxyguanosine	Deoxyguanylate monophosphate (dGMP)
Thymine (T)	Deoxythymidine	Deoxythymidylate monophosphate (dTMP)

Table 2. Names of DNA bases, nucleosides, and nucleotides.

Figure 10 shows how purine nucleotides (A and G) are synthesized. To simplify the molecular diagrams in this and future figures, we follow the snobby chemists' conventions that corners where lines meet or bend indicate a carbon atom unless otherwise noted, and that any extra bonds not shown (4 for carbon, 3 for nitrogen, and 2 for oxygen) are attached hydrogen atoms that we were just too lazy to draw.

The basic idea of purine synthesis is that cells start with a ribose sugar with one phosphate attached, then slowly build the double-ring purine structure by stealing pieces from amino acids and other molecules, creating a weird purine nucleotide called inosine, which is then converted into the more familiar adenosine or guanosine. These nucleotides begin life as RNA nucleotides with blue hydroxyl (OH) groups, but they can be given sex-change operations to become deoxy (blue H only) DNA nucleotides, so you end up with both RNA and DNA versions of A and G nucleotides.

Old RNA and DNA purine nucleotides can be partially broken down and then reused to form new RNA and DNA, which is called the **salvage pathway**, or they can be completely degraded as shown in Fig. 11. Different steps are catalyzed by different enzymes with names in italics. Cells can remove the phosphates and ribose sugars from purine nucleotides, but they cannot easily break down the double ring of purine bases. The best they can do is to chemically modify the double ring to make **uric acid**, which the body eliminates in (you guessed it) urine. In some metabolic diseases, uric acid builds up in the body, causing anything from joint pain (gout) to mental aberrations (Lesch-Nyhan syndrome).

Whereas purine bases are built by adding pieces to a ribose phosphate, pyrimidine bases are built from pieces and only then added to a ribose phosphate, as shown in Fig. 12. They first appear as an unusual base called orotate, then become uridine, and then get converted to cytidine or thymidine if necessary. As with purines, pyrimidine nucleotides are initially made as RNA versions, then converted to DNA versions when necessary.

Old RNA and DNA pyrimidine nucleotides can also be partially broken down and then reused to form new RNA and DNA via the salvage pathway. Or if a cell wants to degrade them, it can remove the phosphate and ribose groups and then break open the pyrimidine single ring structure, creating amino acids that can be used in various ways (Fig. 13).

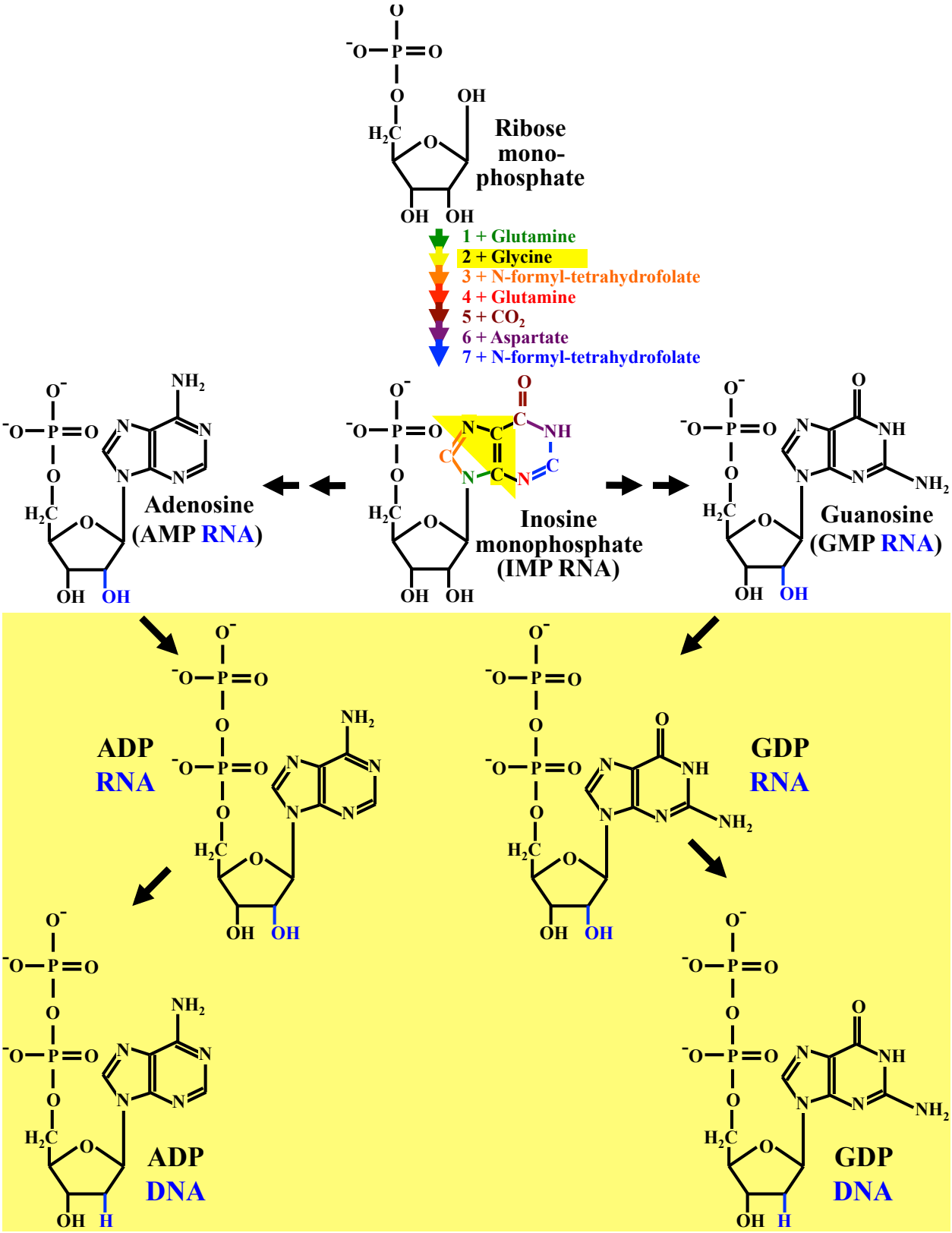


Fig. 10. Synthesis of purine nucleotides.

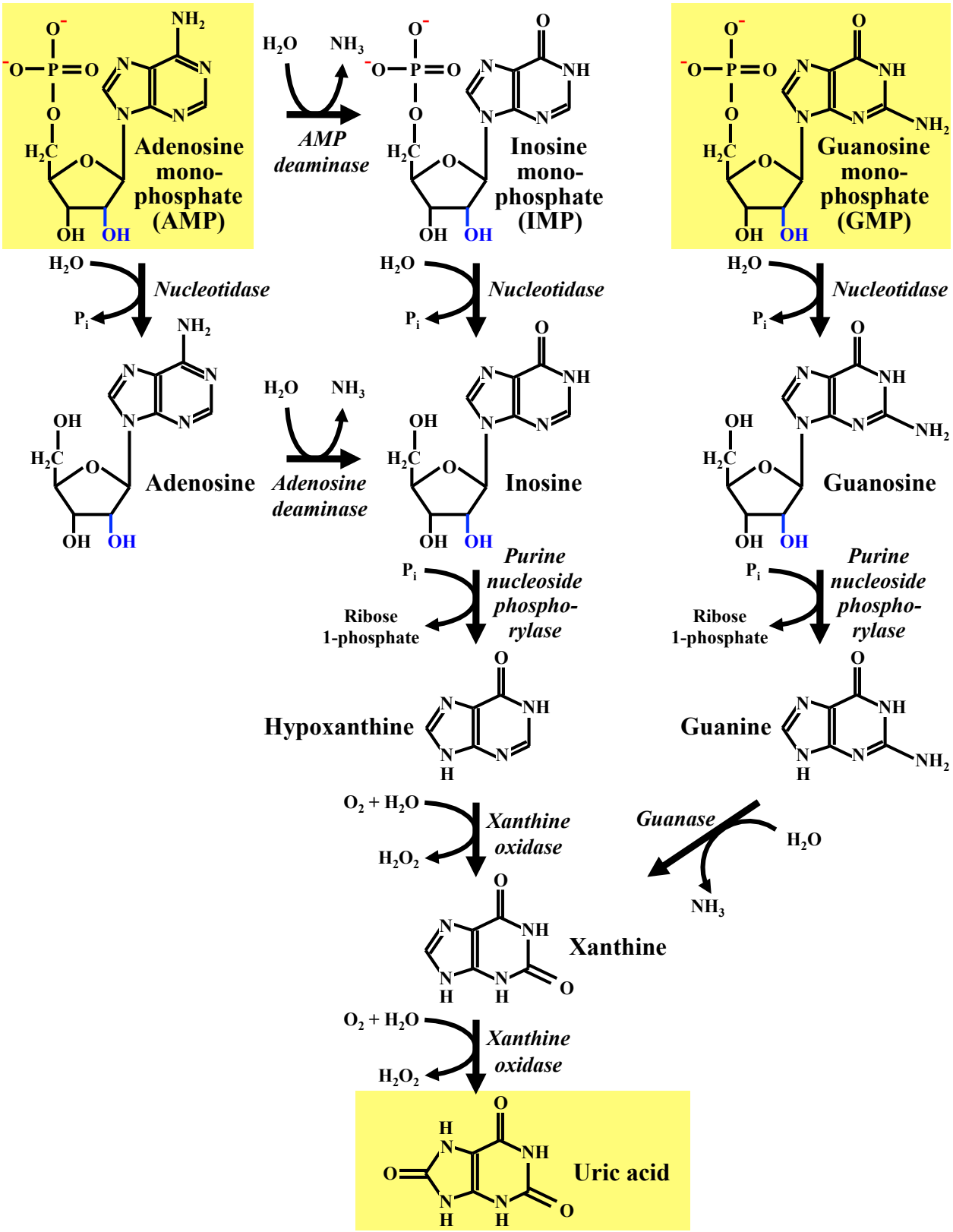


Fig. 11. Degradation of purine nucleotides.

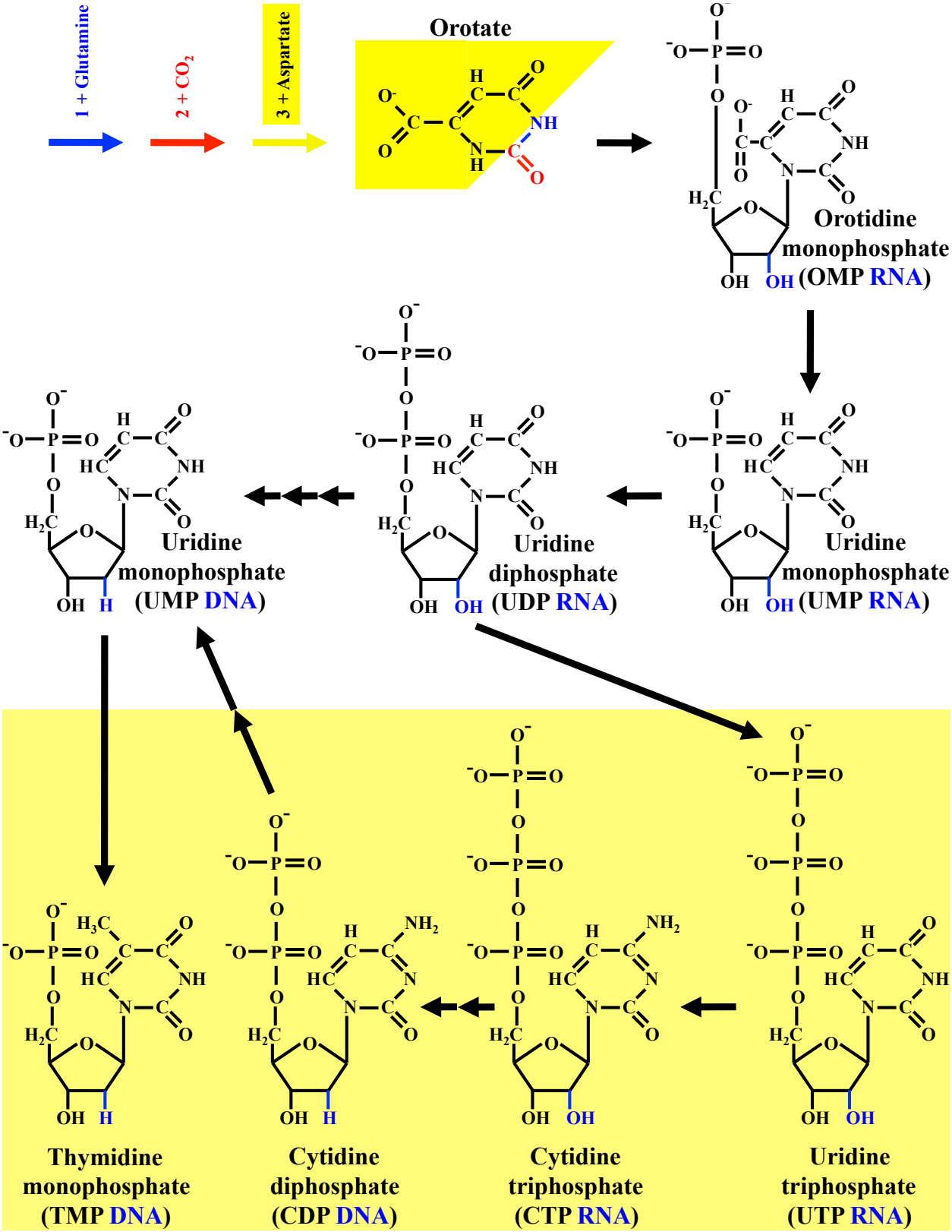


Fig. 12. Synthesis of pyrimidine nucleotides.

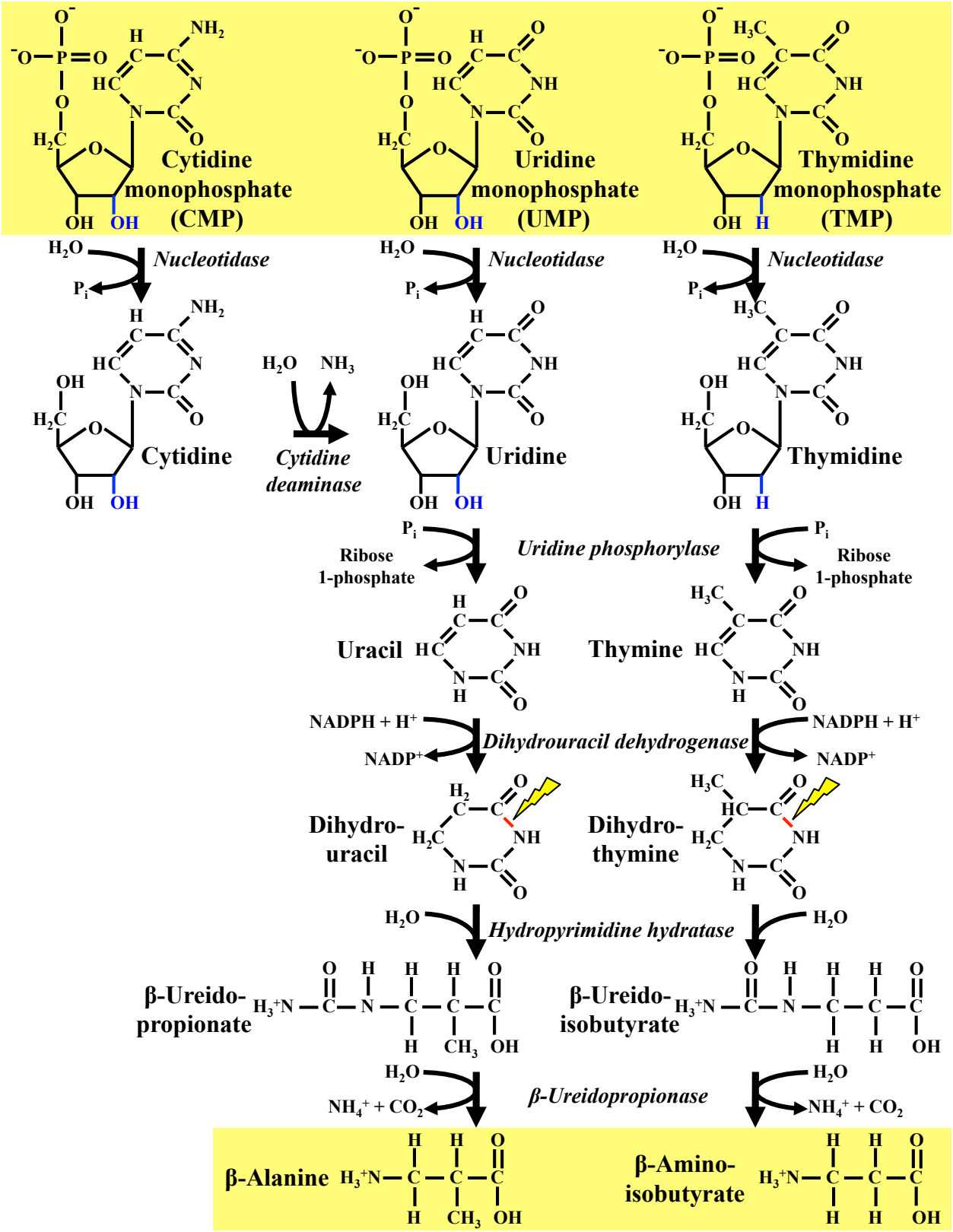


Fig. 13. Degradation of pyrimidine nucleotides.

2.2 Creative Uses for Nucleotides

In addition to using strands of nucleotides to store genetic information as DNA or RNA, cells use individual nucleotides in very creative ways for other purposes:

- **Energy storage.** As shown in Fig. 14, energy (measured in kilojoules per mole of molecules, or kJ/mol) can be released by whacking off one of the phosphate groups (a phosphorous atom surrounded by oxygen atoms, dubbed inorganic phosphate or P_i for short) to convert adenosine triphosphate (ATP) to adenosine diphosphate (ADP) or to convert guanosine triphosphate (GTP) to guanosine diphosphate (GDP):

$$\mathrm{ATP} + \mathrm{H_2O} \iff \mathrm{ADP} + \mathrm{P_i} + 30.5\,\mathrm{kJ/mol} \tag{7}$$

$$\mathrm{GTP} + \mathrm{H_2O} \iff \mathrm{GDP} + \mathrm{P_i} + 30.5\,\mathrm{kJ/mol} \tag{8}$$

  Reactions (7) and (8) can also be run in reverse. As will be explained in Section 7, specialized organelles called mitochondria in plant, animal, and fungal cells (or similar structures in bacteria) use the chemical energy from sugars and other nutrients to convert ADP to ATP. A wide variety of enzymes in cells are powered by converting the ATP back to ADP (or occasionally GTP to GDP, where the GTP gets made by mooching phosphates off extra ATP made by the mitochondria).

- **Intracellular signaling.** As shown in Fig. 15, adenosine or guanosine nucleotides can be made circular or cyclic by having the same phosphate that is glued to the upstream 5' end also glom onto the downstream 3' end. Cells temporarily synthesize (using specialized cyclase enzymes) and then when finished degrade (using phosphodiesterase enzymes) these cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) molecules as a way of sending signals within a cell, sort of like sending smoke rings as signals.

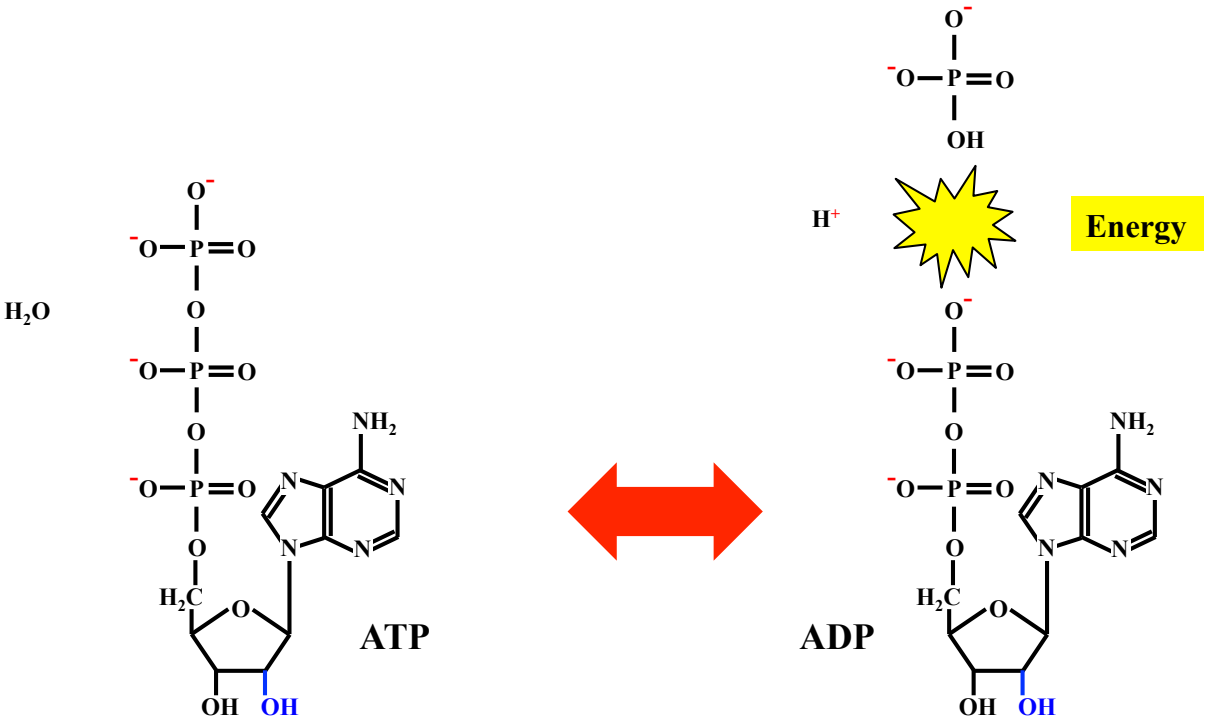
- **Electron transport.** Nucleotides are modified in weird ways to create carrier molecules or coenzymes that can transport electrons (and protons and some energy, measured in electron-volts or eV) from one reaction to another. This will be especially important in Sections 7–9. As shown in Figs. 16–17, there are three different nucleotide-derived electron carriers that all do basically the same job: Nicotinamide Adenine Dinucleotide (NAD^+ or NADH), Nicotinamide Adenine Dinucleotide Phosphate ($NADP^+$ or NADPH), and Flavin Adenine Dinucleotide (FAD or $FADH_2$):

$$\mathrm{NAD^+} + 2\mathrm{H^+} + 2\mathrm{e^-} + 0.320\,\mathrm{eV} \iff \mathrm{NADH} + \mathrm{H^+} \tag{9}$$

$$\mathrm{NADP^+} + 2\mathrm{H^+} + 2\mathrm{e^-} + 0.315\,\mathrm{eV} \iff \mathrm{NADPH} + \mathrm{H^+} \tag{10}$$

$$\mathrm{FAD} + 2\mathrm{H^+} + 2\mathrm{e^-} + 0.219\,\mathrm{eV} \iff \mathrm{FADH_2} \tag{11}$$

(a) Adenosine triphosphate (ATP) and adenosine diphosphate (ADP)



(b) Guanosine triphosphate (GTP) and guanosine diphosphate (GDP)

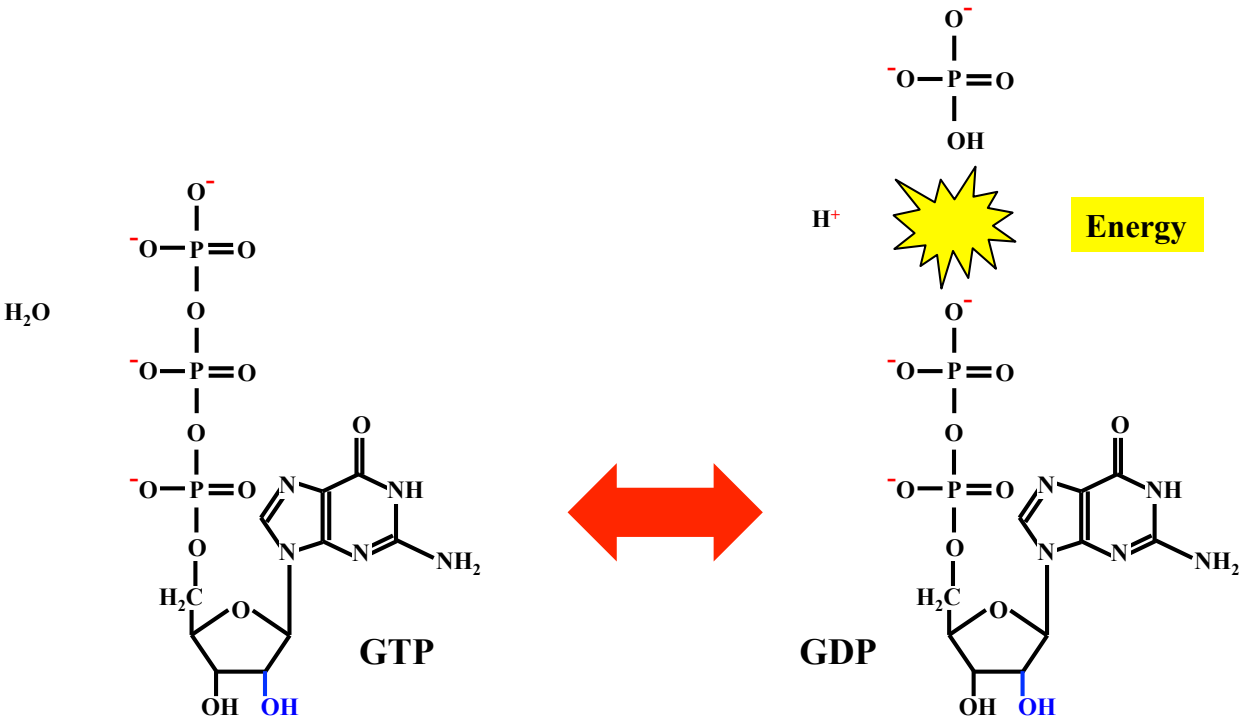


Fig. 14. Energy storage and release by (a) adenosine triphosphate (ATP)/adenosine diphosphate (ADP) and (b) guanosine triphosphate (GTP)/guanosine diphosphate (GDP).

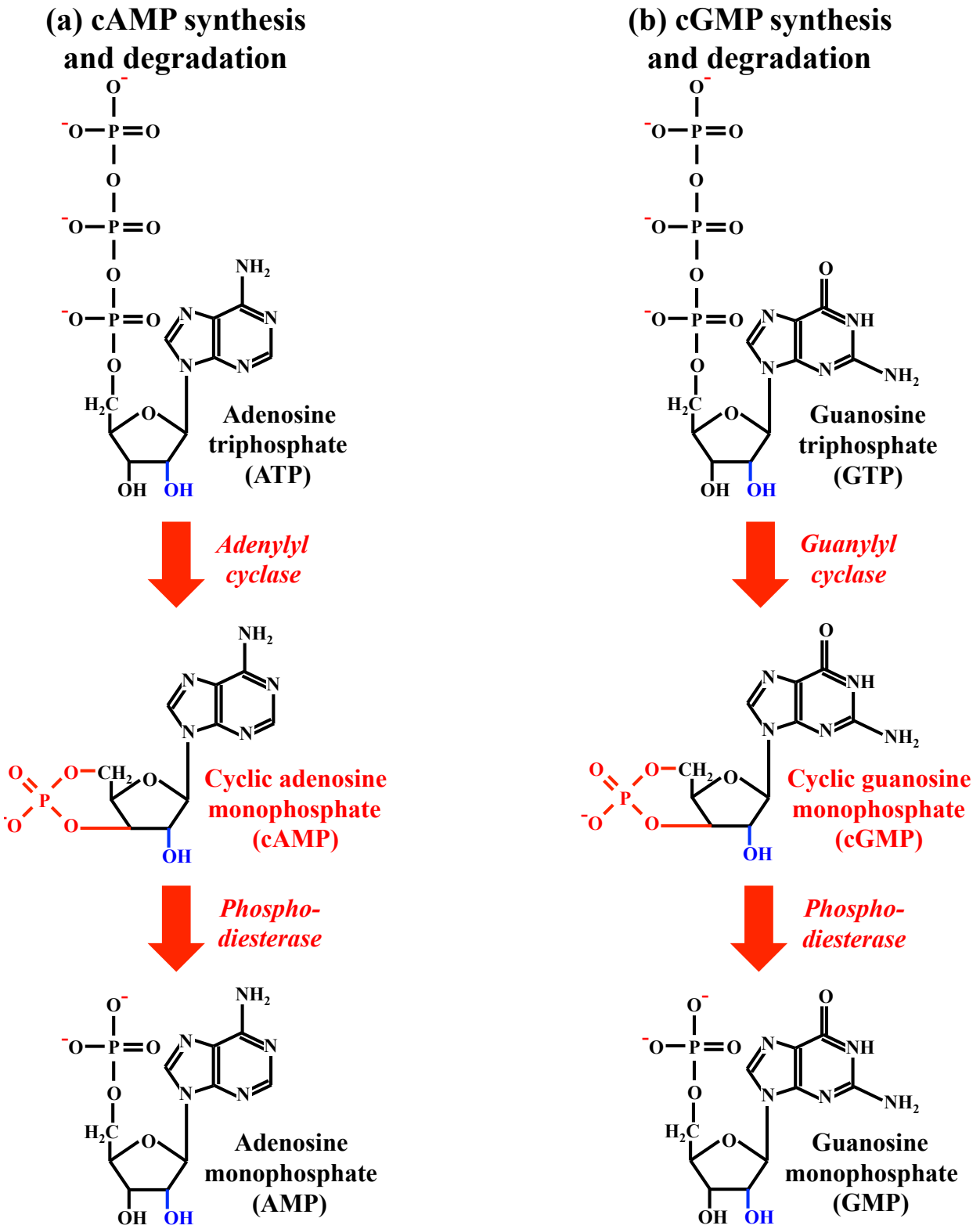


Fig. 15. Synthesis and degradation of (a) cyclic adenosine monophosphate (cAMP) and (b) cyclic guanosine monophosphate (cGMP).

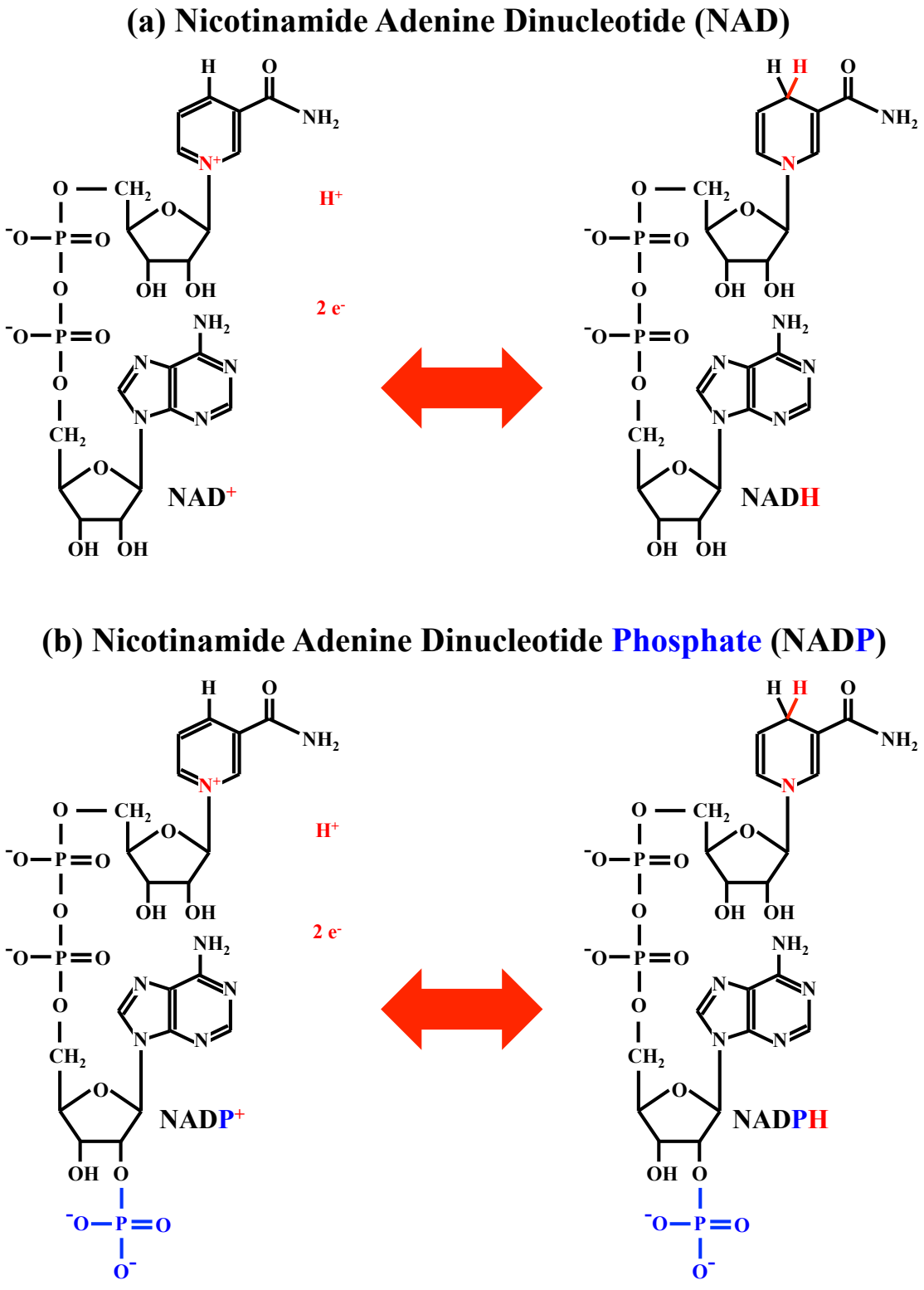


Fig. 16. Two nucleotide-derived molecules that are used to transport electrons and protons: (a) Nicotinamide Adenine Dinucleotide (NAD^+ or NADH) and (b) Nicotinamide Adenine Dinucleotide Phosphate ($NADP^+$ or NADPH).

Flavin Adenine Dinucleotide (FAD)

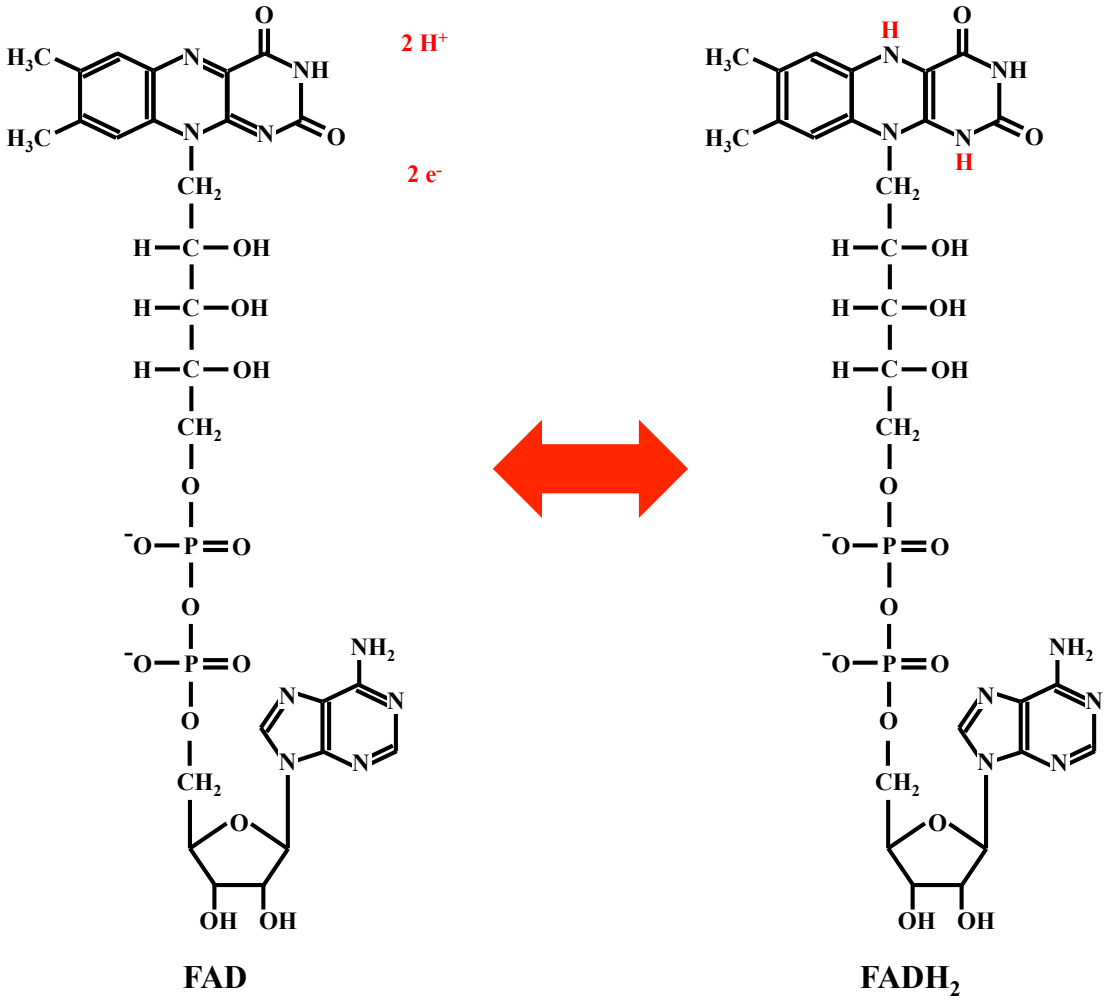


Fig. 17. Flavin Adenine Dinucleotide (FAD or $FADH_2$) is another nucleotide-derived molecule that is used to transport electrons and protons.

2.3 DNA

Individual DNA nucleotides can be strung together or polymerized to form a strand of DNA. As illustrated in Fig. 18, the nucleotides start in their triphosphate forms. The downstream 3' end of one nucleotide gloms onto the upstream 5' end of the next nucleotide, but two phosphates of that second nucleotide are broken off to help provide energy for the reaction. This gives DNA strands a "backbone" of alternating ribose sugar and single phosphate groups, with bases (A, C, G, or T) attached to each ribose. A DNA strand can also be hydrolyzed or split apart into individual nucleotides. Polymerase enzymes make DNA strands, and DNase enzymes split them apart; both will be covered in great gory detail in *Molecular Biology and Genetics*.

Figure 19 gives a two-dimensional depiction of how two DNA strands can interact. The dotted lines show hydrogen bonds, or weak attractive forces between specific bases that causes **base pair** formation or **base pairing**. A and T bases fall into each other's arms with two hydrogen bonds, and C and G nucleotides gravitate to each other with three hydrogen bonds. The other possible combinations of bases just ignore each other, so nucleotide dating reality TV shows would be rather boring. Note that one DNA strand goes 5' to 3' one way, and the other DNA strand goes 5' to 3' the other way. If the nucleotide sequences of the two strands line up so that every A on one side has a T on the other side, and every C on one side has a G on the other side, the sequences of the two DNA strands are said to be **complementary**.

Just so the nice two-dimensional image of Fig. 17 doesn't make you misunderestimate (as "W." would say) the complexity of the double-stranded DNA structure, Fig. 20 shows a more realistic three-dimensional image of DNA that we have stolen from Wikipedia (hey, there are only so many hours in the day). The sugar-phosphate backbone of DNA curves, so double-stranded DNA forms a double helix or spiral staircase structure, with the backbones of the two strands as the sides of the spiral staircase, and the base pairs of complementary nucleotides as the steps of the staircase.

We could geek out about DNA for many, many more pages, but we will save that for *Molecular Biology and Genetics*.

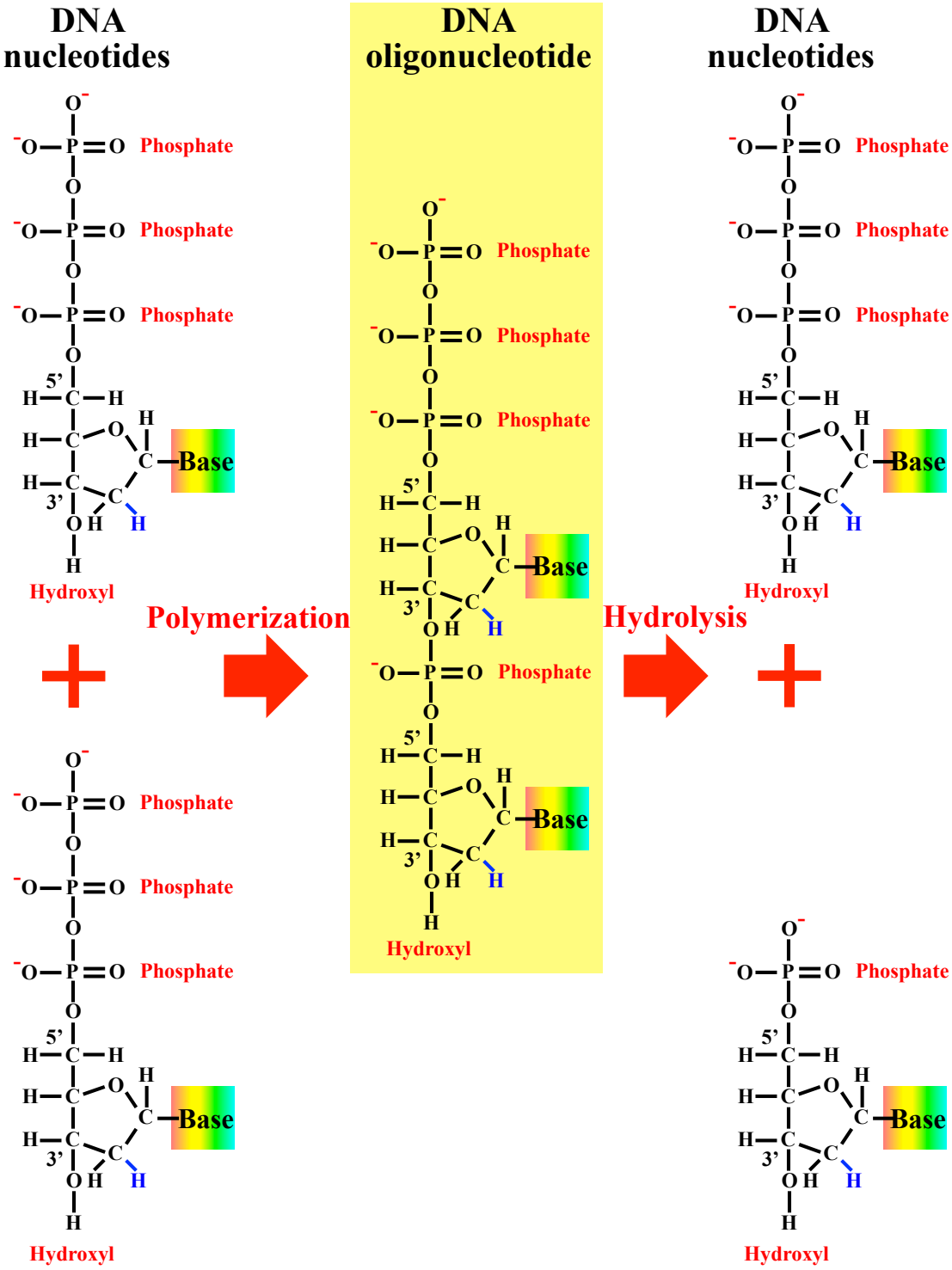


Fig. 18. Polymerization of individual DNA nucleotides to form a DNA oligonucleotide strand, and hydrolysis of the DNA strand to release individual DNA nucleotides.

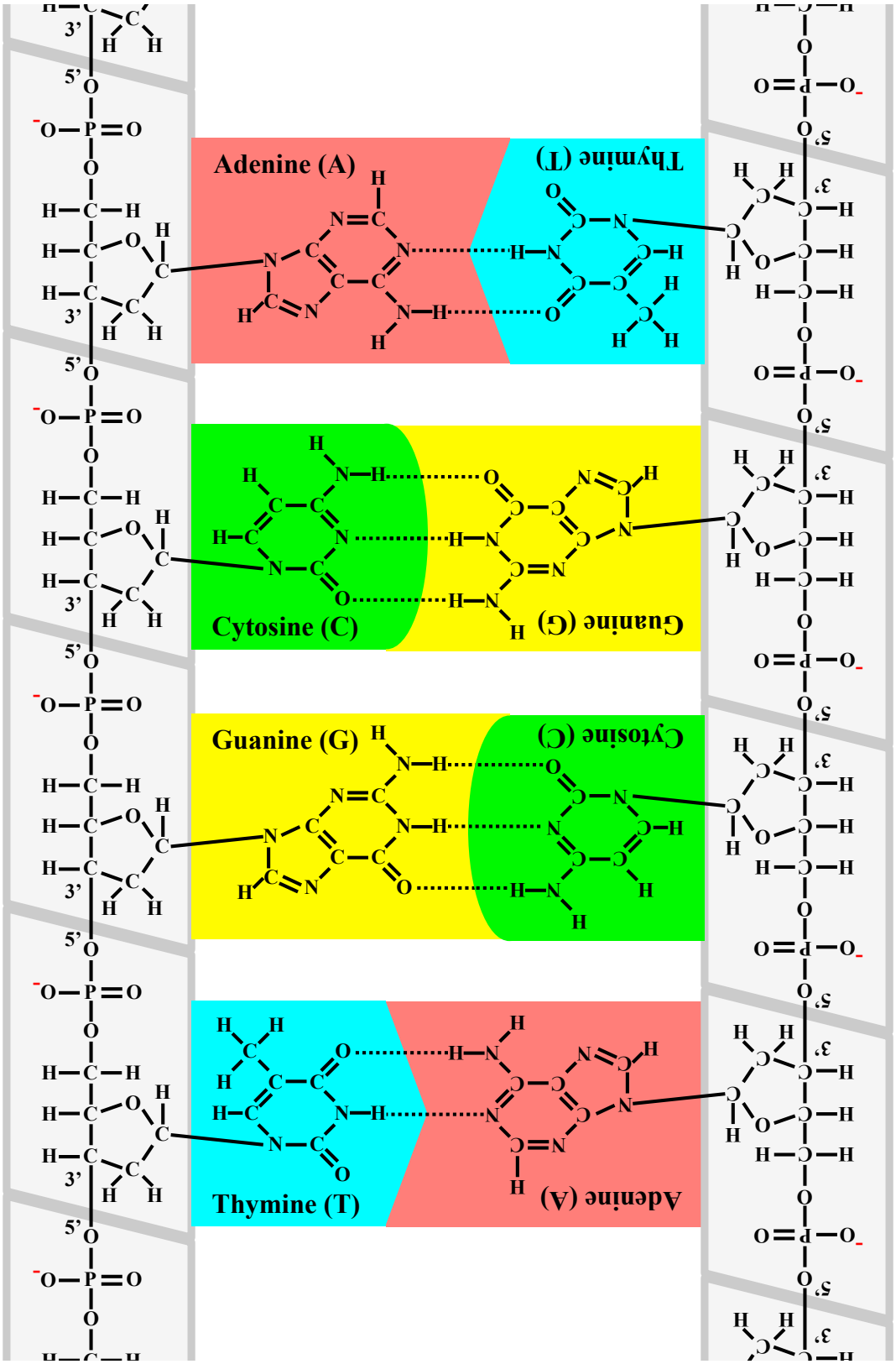


Fig. 19. Two-dimensional depiction of two complementary DNA strands, showing hydrogen bonds (dotted lines) between the base pairs.

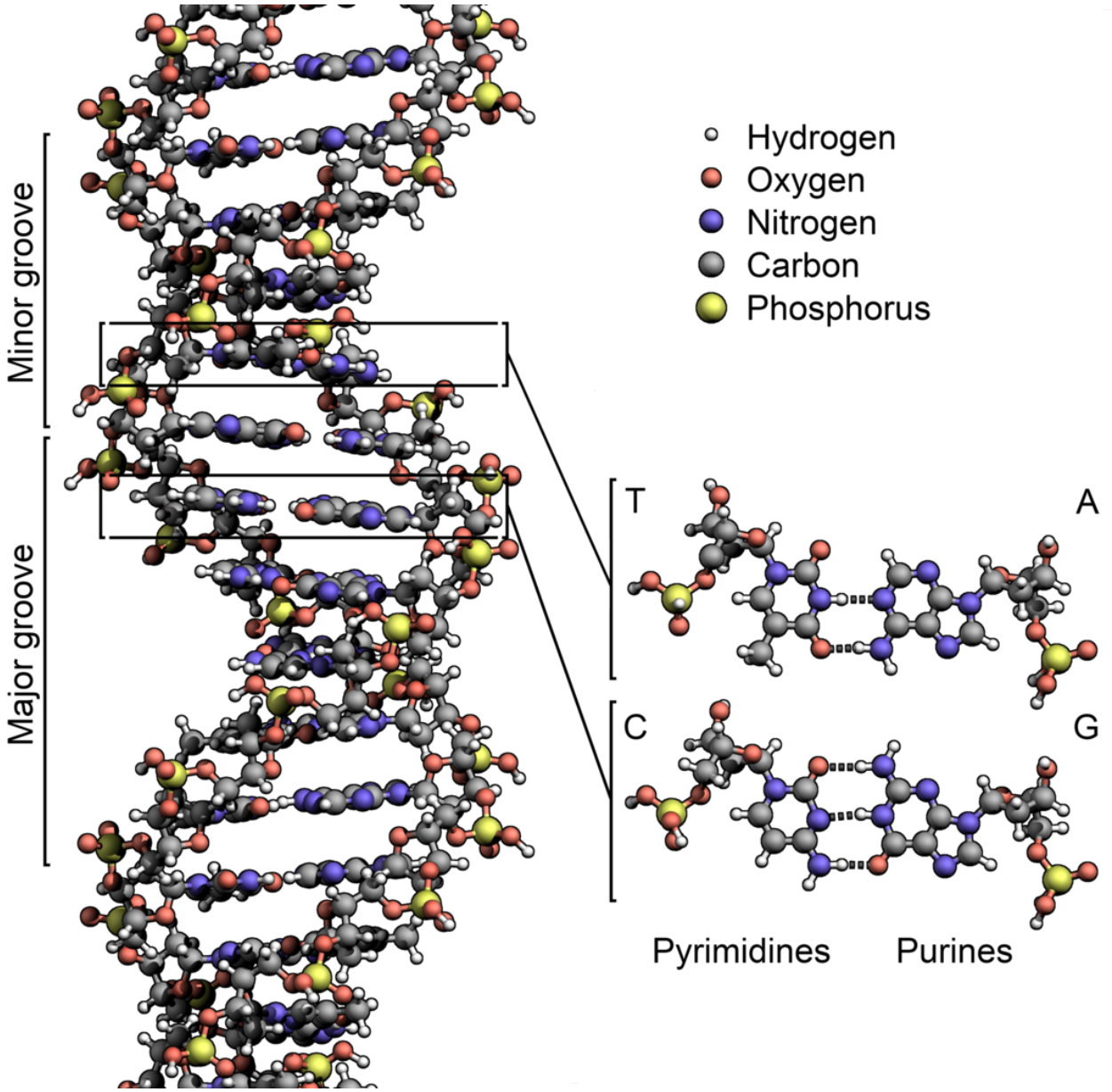


Fig. 20. Three-dimensional structure of double-stranded DNA (public-domain image from Wikipedia, https://en.wikipedia.org/wiki/DNA).

2.4 RNA

RNA is nearly identical to DNA, but each RNA nucleotide has a dangling hydroxyl (blue OH group in Fig. 21) where DNA just has a hydrogen (H), and RNA uses uracil (U) bases wherever DNA uses thymine (T) bases. Just as DNA nucleotides are strung together by DNA polymerase enzymes and broken apart by DNase enzymes, RNA nucleotides are strung together by RNA polymerases and broken apart by RNases (Fig. 21). The dangling hydroxyl groups make RNA degrade much more rapidly than DNA would in the same environment, so cells generally use DNA to encode their complete genetic blueprint and RNA to make temporary copies of individual genes as needed.

As shown in Fig. 22, complementary RNA and DNA strands can bind to form an RNA-DNA hybrid, with each RNA U base-pairing with a DNA A. Likewise, two complementary RNA strands can also bind to each other.

There are at least four different types of RNA strands that play roles in cells:

- **Ribosomal RNA (rRNA)** is a major component of ribosomes, the cellular machines that make proteins. As shown in Fig. 23(a), prokaryotic (bacterial cell) ribosomes are composed of a large subunit that contains two rRNAs and 31 proteins, and a small subunit that contains one rRNA and 21 proteins. As illustrated in Fig. 23(b), eukaryotic (animal, plant, and fungal cell) ribosomes are composed of a large subunit that contains three rRNAs and 50 proteins, and a small subunit that contains one rRNA and 33 proteins. Ribosomal RNAs are single-stranded, but they can loop back on themselves in certain places to create short double-stranded RNA regions that stabilize the overall structure. Regions where RNA loops back and binds to itself are called **hairpins** because of their analogous shape.

- **Transfer RNA (tRNA)** grabs individual amino acids and brings them to the ribosome, where they are glued together to form proteins, as shown in Fig. 23(c). Different types of tRNA grab different amino acids. Each tRNA is single-stranded but forms a sort of cross shape due to hairpins.

- **Messenger RNA (mRNA)** is a single-stranded RNA copy of a DNA gene. Each mRNA is made in the cell's nucleus and then shipped out of the nucleus to the surrounding ribosomes, where its genetic instructions are used to create the corresponding protein, as illustrated in Fig. 23(c). Base-pairing between every three nucleotides (collectively called a **codon**) of the mRNA and three complementary nucleotides (an **anticodon**) on the right tRNA specify which tRNA-guided amino acid should be incorporated into the new protein next.

- **Small interfering RNA (siRNA)** includes various types of short single- or double-stranded RNAs that bind to and interfere with other RNAs or with DNA, as another mechanism that cells use to control the activity of their individual genes.

As with DNA, RNA will be covered in vastly more detail in *Molecular Biology and Genetics*.

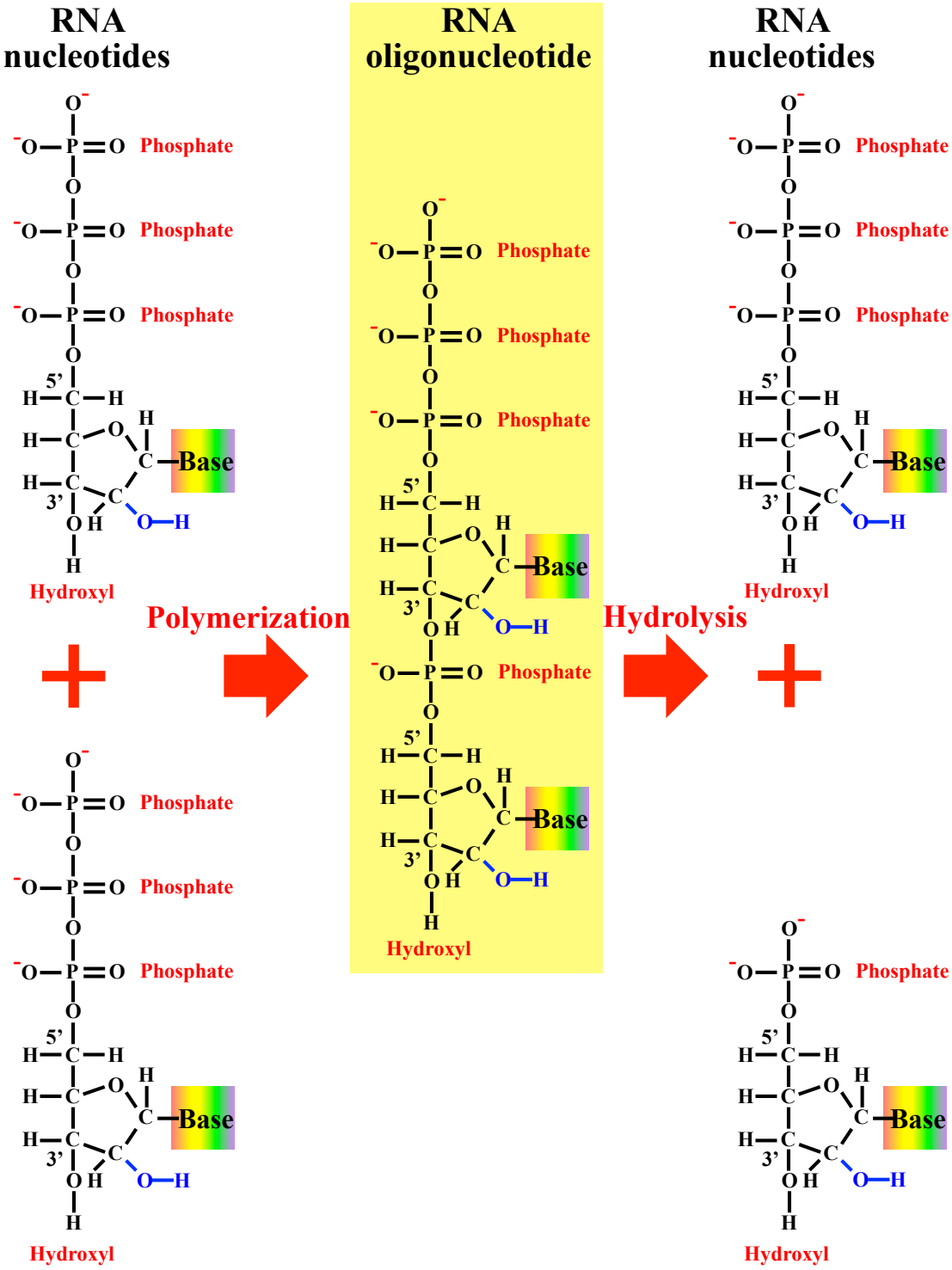


Fig. 21. Polymerization of individual RNA nucleotides to form an RNA oligonucleotide strand, and hydrolysis of the RNA strand to release individual RNA nucleotides.

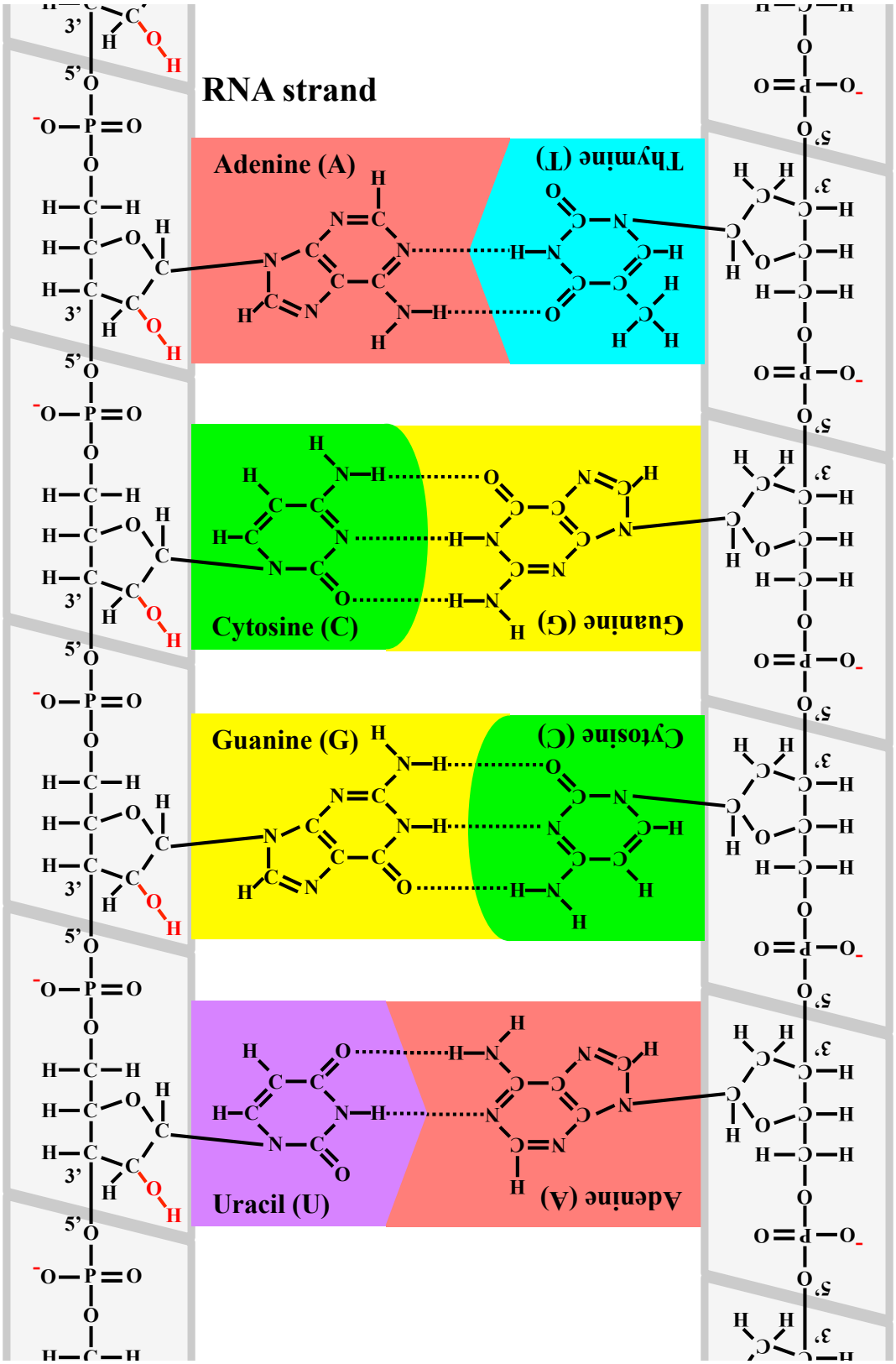


Fig. 22. Two-dimensional depiction of complementary RNA (left side) and DNA (right side) strands, showing hydrogen bonds (dotted lines) between the base pairs.

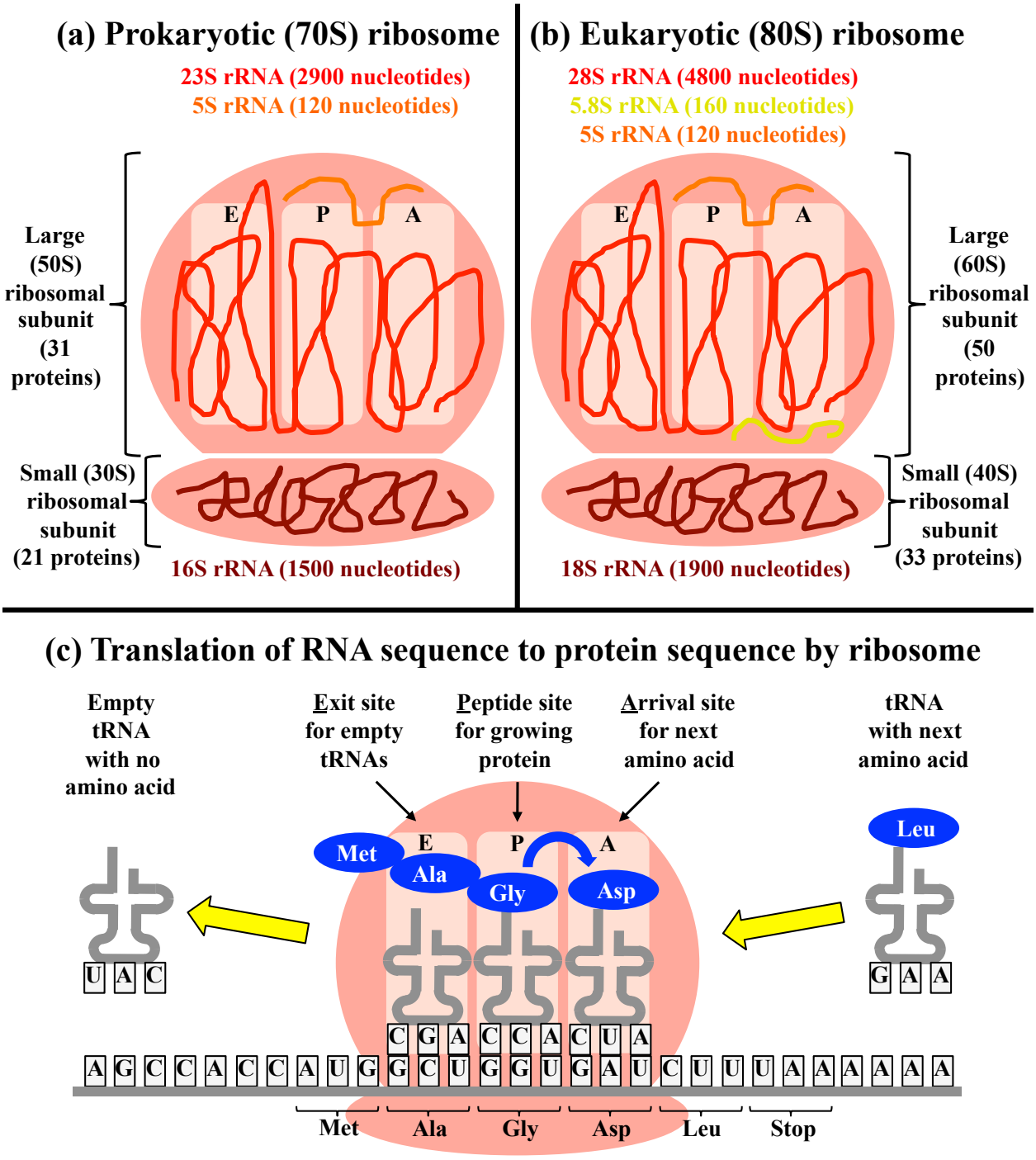


Fig. 23. Ribosomes. **(a)** Prokaryotic ribosomes are composed of a large subunit (which contains two ribosomal RNAs or rRNAs and 31 proteins) and a small subunit (which contains one rRNA and 21 proteins). **(b)** Eukaryotic ribosomes are composed of a large subunit (which contains three rRNAs and 50 proteins) and a small subunit (which contains one rRNA and 33 proteins). **(c)** Despite their differences in size, prokyarotic and eukaryotic ribosomes work in a similar fashion to create proteins by translating a messenger RNA (mRNA) sequence into the amino acid sequence of the corresponding protein. Transfer RNAs (tRNAs) bring each new amino acid to the ribosome.

3 Amino Acids and Proteins

This section will cover how individual amino acids are synthesized and degraded in cells, and then how amino acids are strung together to create proteins.

3.1 Amino Acid Synthesis and Degradation

Amino acids have an amine or ammonia (NH_2 or NH_3^+) group at one end that assumes a positively charged state at normal physiological conditions (pH$\sim$7), a carboxylic acid (COOH or COO^- with double bonds between one of the oxygens and the carbon) on the other end that assumes a negatively charged state at normal conditions, and a CH with a side chain R in the middle. There are 20 different common amino acids, which differ from each other in whether the side chain R is anything from a simple hydrogen to complex rings of atoms (Figs. 24–27).

10 of the amino acids are made starting with $\alpha-$ketoglutarate or oxaloacetate, as shown in Fig. 28. Those are two components of the citric acid cycle in mitochondrial respiration that will be covered in Section 7. For now all you have to know is that there is a lot of mitochondrial respiration, so there are a lot of these $\alpha-$ketoglutarate or oxaloacetate starting components floating around. By acquire amine groups and being transmogrified in various other ways, with each step catalyzed by a different enzyme, these starting components are gradually turned into amino acids. Humans lack the enzymes needed for the reaction arrows shown in red, so we cannot make the red amino acids from scratch. Those are called **essential amino acids**, since we must acquire them by eating plants that make them, or at least animals that have eaten plants that made them. When cells get bored playing with particular amino acids, they degrade them by converting them back into $\alpha-$ketoglutarate or oxaloacetate and stuffing them back into the citric acid cycle in mitochondria.

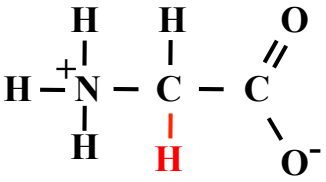
The other 10 common amino acids are made using starting components derived from the glycolysis/gluconeogenesis pathway and pentose phosphate pathway, as illustrated in Fig. 29. These are pathways involved in metabolizing sugars and will be covered in Section 5, but again the main point is that cells have a lot of these starting ingredients lying around. And again, various enzymes add amine groups and make other changes to convert these starting ingredients into the desired amino acids. Humans lack enzymes for the red arrows shown in Figs. 28–29, so several of these are also essential amino acids that must be acquired from things we eat. Any unwanted amino acids can be degraded by the reverse processes and dumped back into the sugar metabolism pathways.

The whole question of where amine groups come from (for amino acid synthesis) and go to (for amino acid degradation) was swept under the rug like so many dust bunnies in Figs. 28 and 29, and now it is time for those killer dust bunnies to emerge and attack in Fig. 30. Transaminase and glutamate dehydrogenase enzymes can pull amine groups off one molecule and stick them on another to create or degrade amino acids, or they can release the amine groups as ammonia (NH_3). The urea cycle illustrated in Fig. 30 collects that waste ammonia buildup and converts it into urea, which is eliminated from the body via (yup) urine. Who knew there was so much fascinating science in pee?

Any compulsive nitpickers ogling Fig. 30 will note that human cells do make some arginine via the urea cycle. However, we don't make enough of it, so sorry, arginine is still an essential amino acid and you still have to eat your veggies.

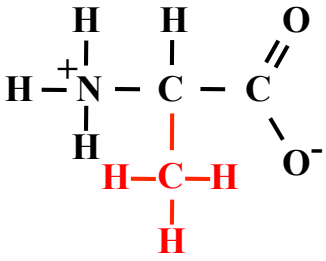
Amino acids with neutral nonpolar sidechains

Glycine (Gly, G)

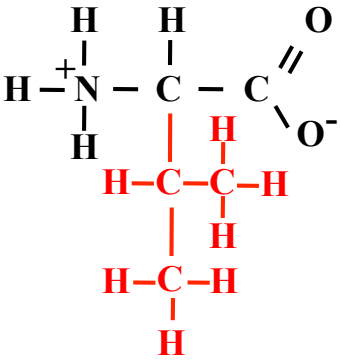


Glycine has no side chain, so it is the most flexible amino acid in proteins.

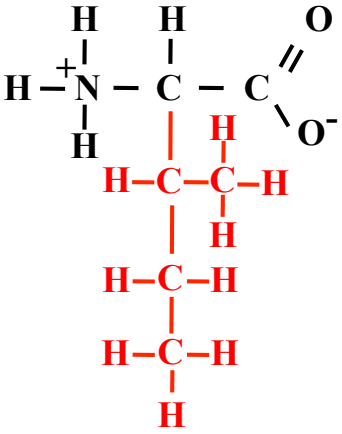
Alanine (Ala, A)



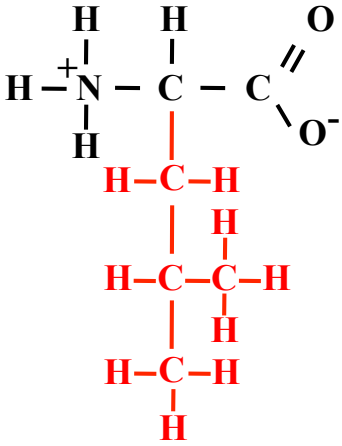
Valine (Val, V)



Isoleucine (Ile, I)

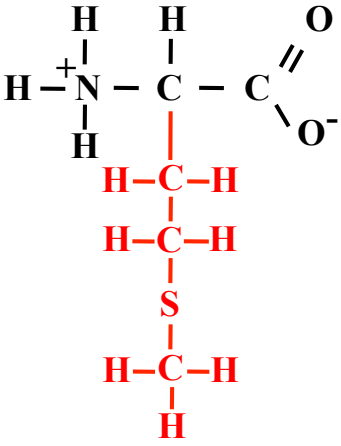


Leucine (Leu, L)



The larger the hydrocarbon side chain, the more hydrophobic the amino acid.

Methionine (Met, M)

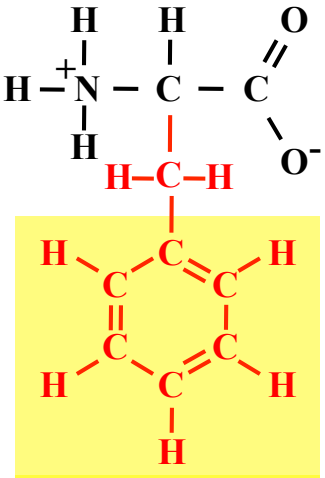


Proteins generally start with a methionine, but they may also contain other methionines in their sequence. Methionine contains a sulfur atom but doesn't do much with it.

Fig. 24. Amino acids with neutral nonpolar sidechains.

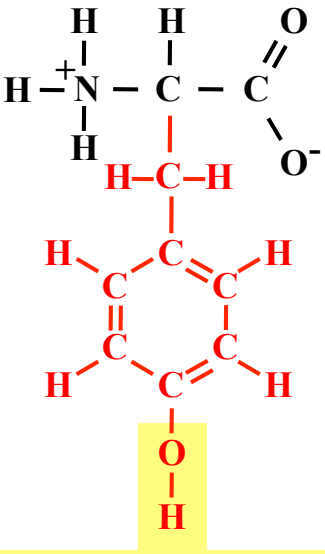
Amino acids with neutral nonpolar sidechains (continued)

Phenylalanine (Phe, F)



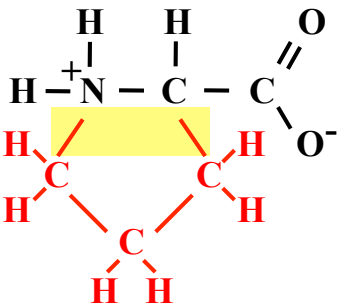
Phenylalanine is very hydrophobic due to the phenyl ring in its side chain.

Tyrosine (Tyr, Y)



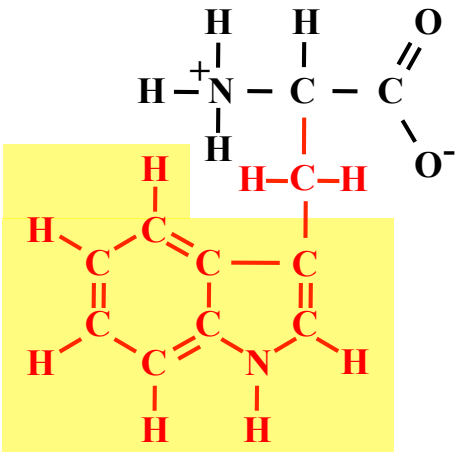
Tyrosine is phenylalanine with a hydrophilic –OH, which offsets the ring's hydrophobicity.

Proline (Pro, P)



Proline's side chain is linked to the amino acid backbone at two different points, so it is the least flexible amino acid in proteins. It often forms exposed bends in folded proteins and is not particularly hydrophobic.

Tryptophan (Trp, W)

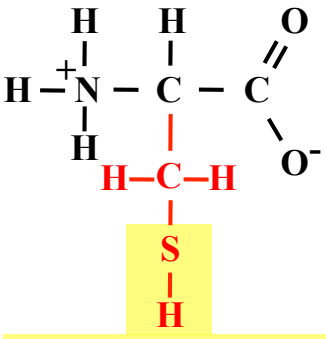


Tryptophan's two rings make it very hydrophobic.

Fig. 25. Amino acids with neutral nonpolar sidechains (continued).

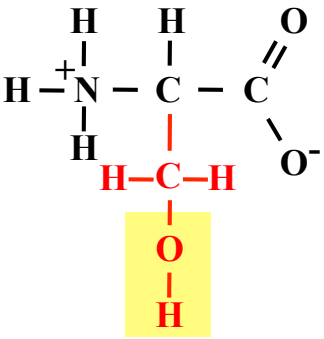
Amino acids with neutral polar sidechains

Cysteine (Cys, C)

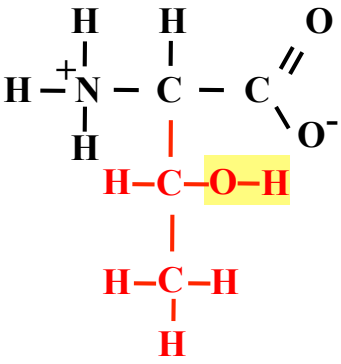


Can easily be oxidized (lose the hydrogen) to form a disulfide (-S-S-) bond with another cysteine, so cysteines are often found on the inside of folded proteins with hydrophobic amino acids.

Serine (Ser, S)

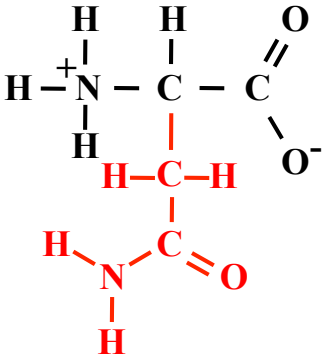


Threonine (Thr, T)

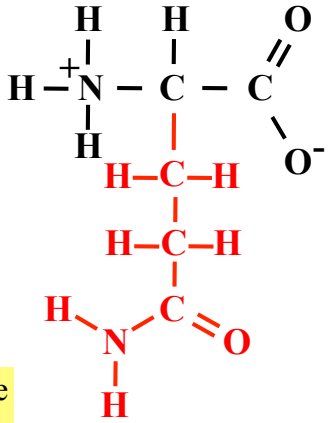


Because serine and threonine have an -OH is their side chain, they are very hydrophilic and somewhat chemically reactive.

Asparagine (Asn, N)



Glutamine (Gln, Q)



The NH_2 and =O groups make asparagine and glutamine polar and hence hydrophilic.

Fig. 26. Amino acids with neutral polar sidechains.

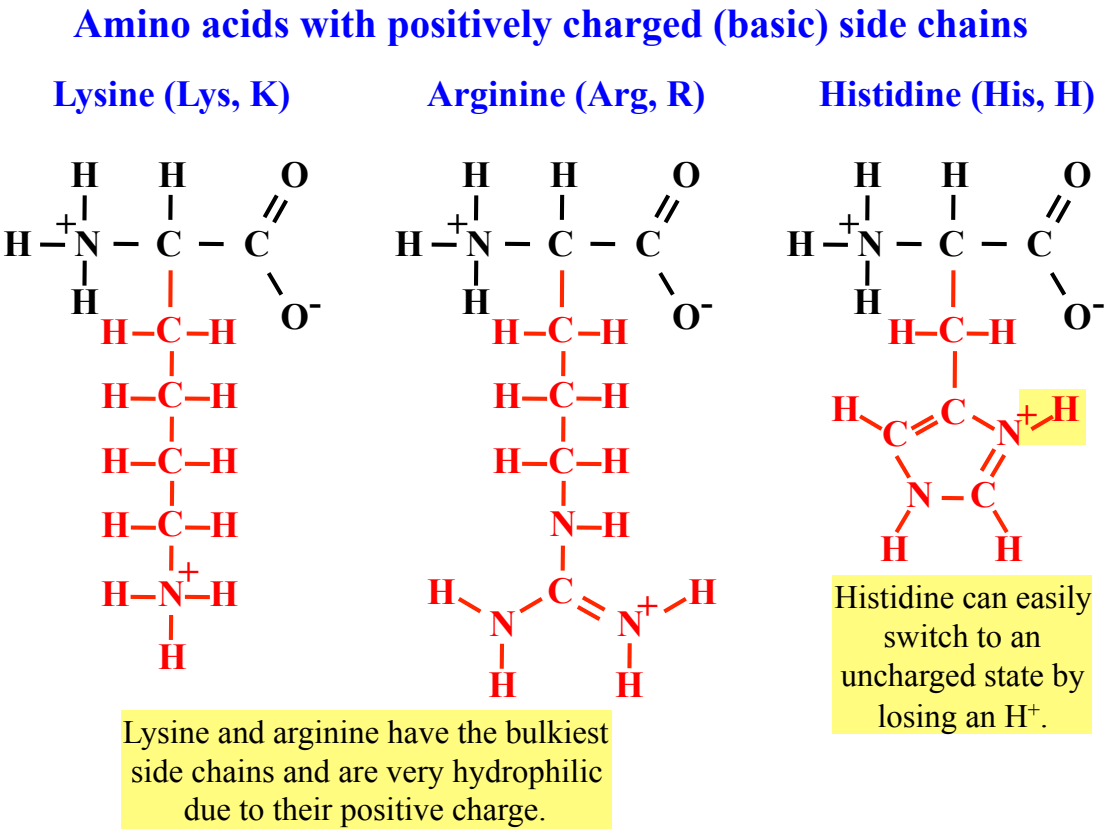


Fig. 27. Amino acids with positively charged (basic) side chains or negatively charged (acidic) side chains.

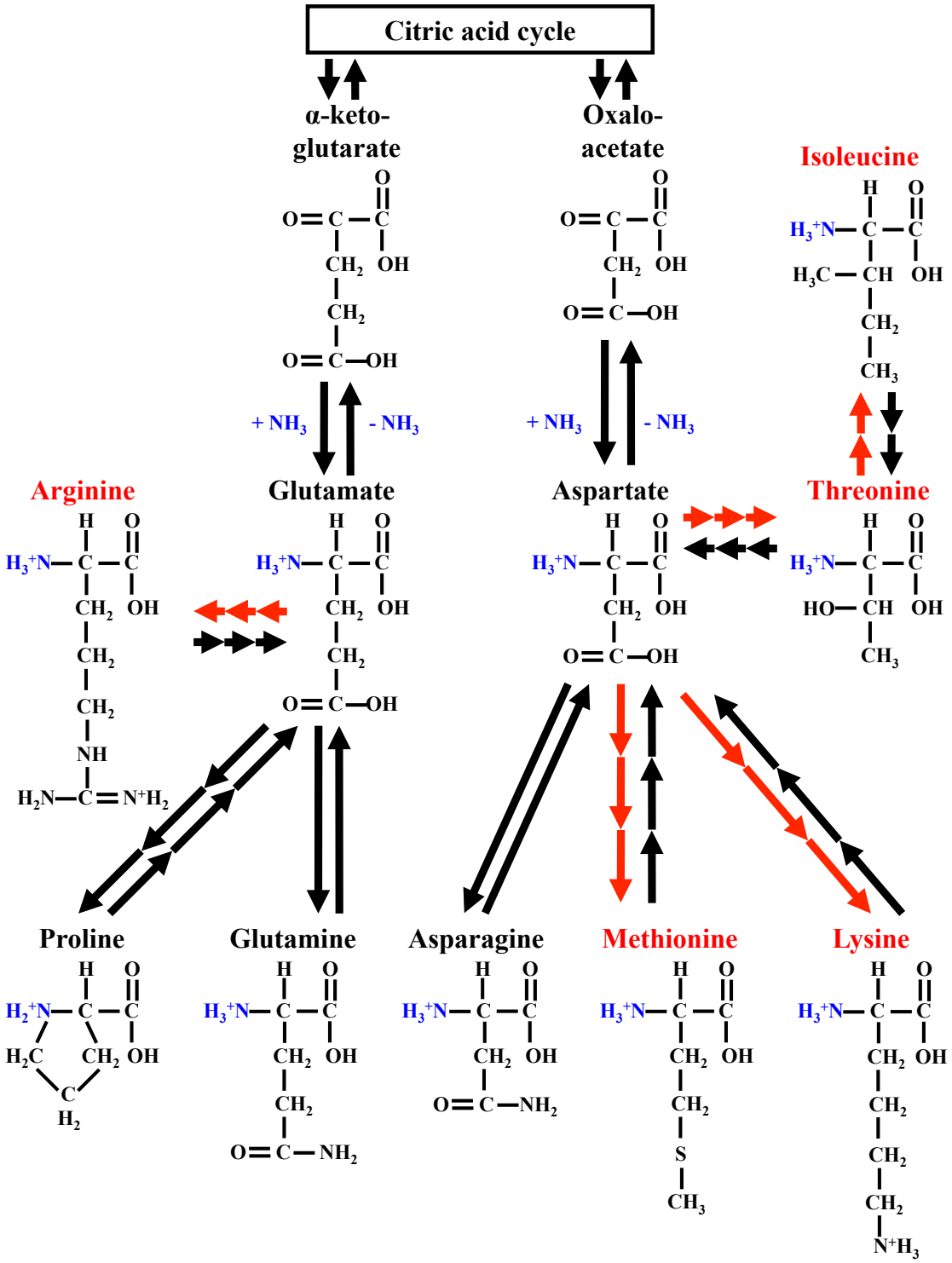


Fig. 28. Synthesis and degradation of amino acids related to the citric acid cycle.

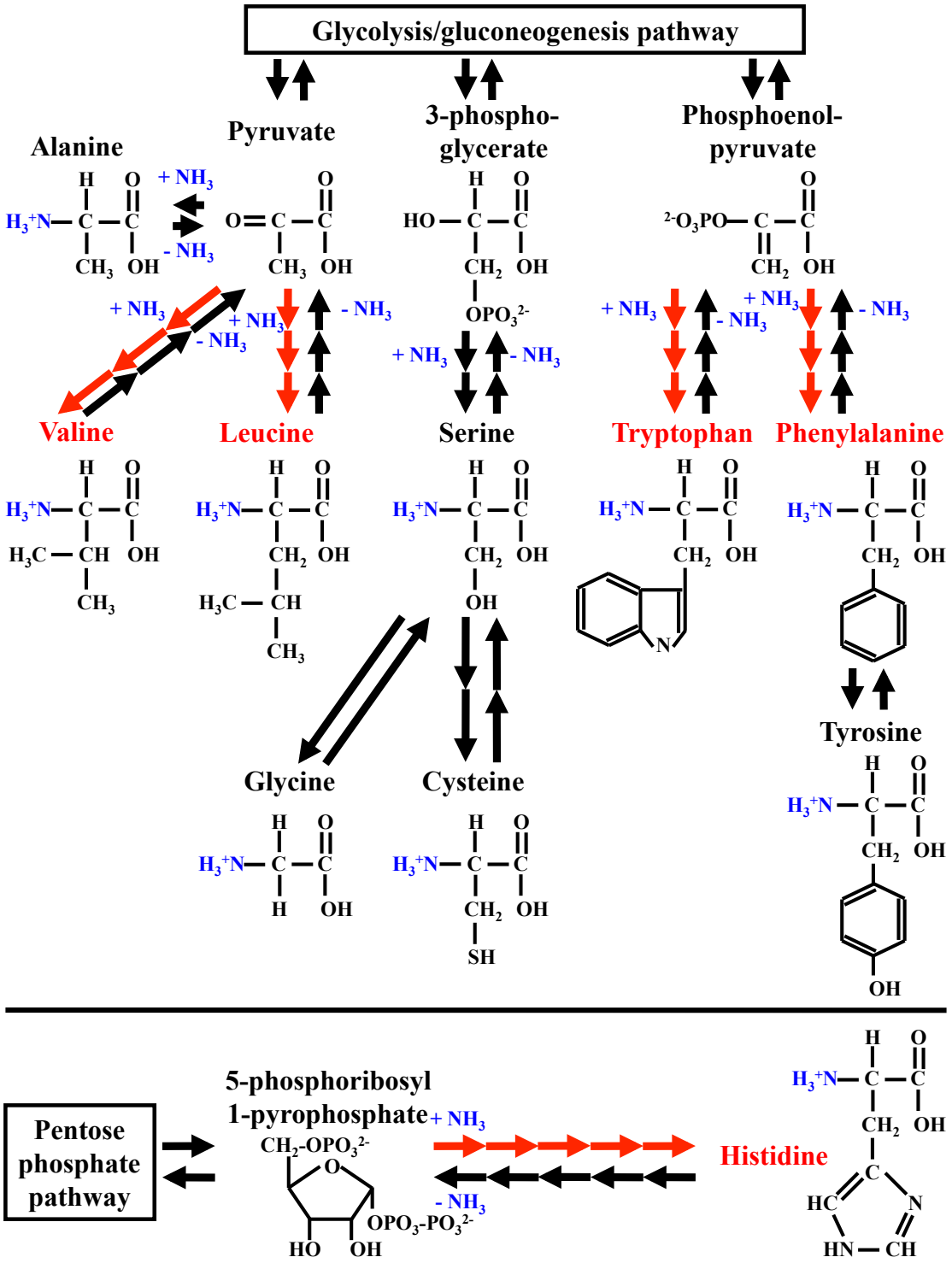


Fig. 29. Synthesis and degradation of amino acids related to the glycolysis/gluconeogenesis pathway and pentose phosphate pathway.

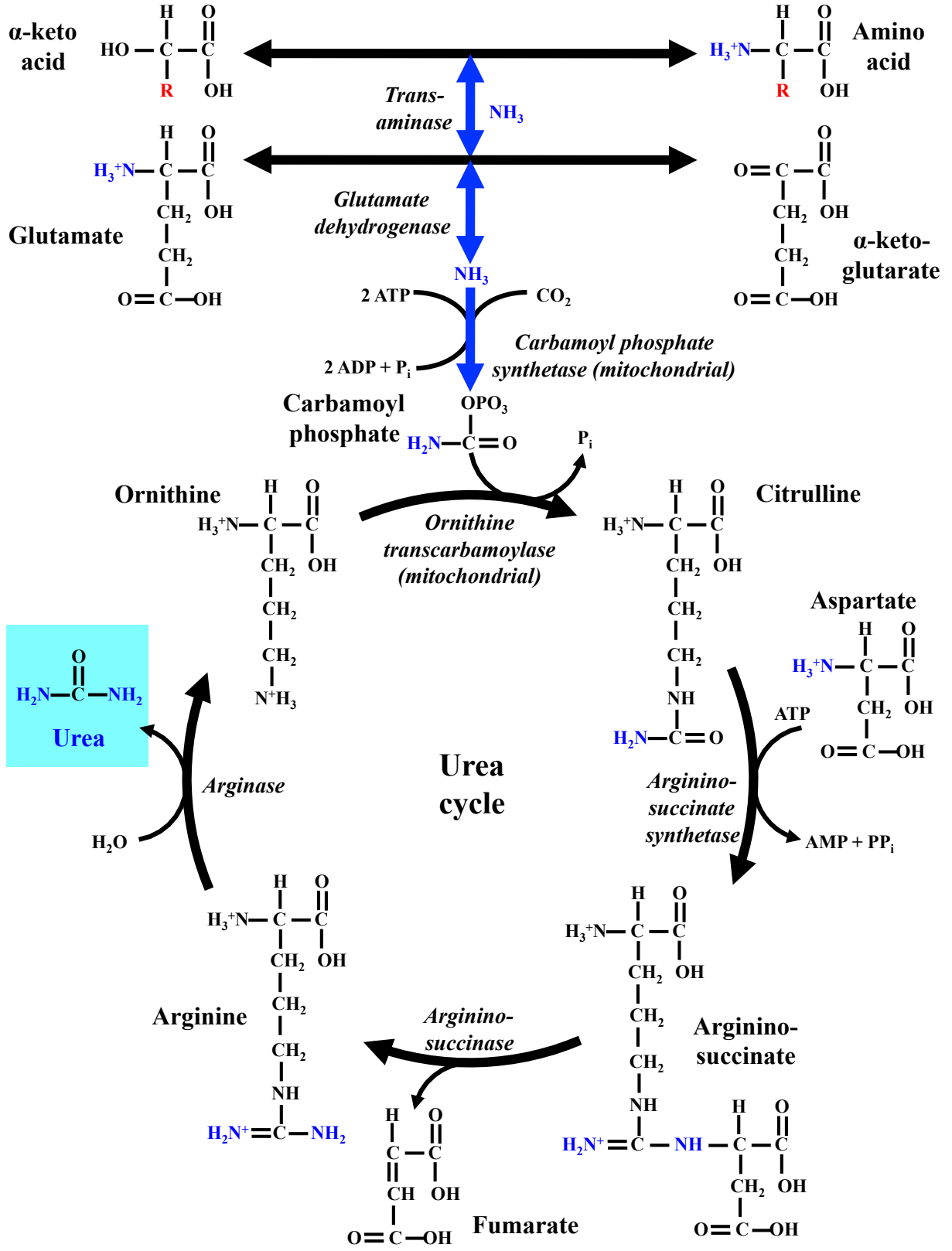


Fig. 30. Urea cycle for disposing of nitrogen removed from amino acids during their degradation.

3.2 Protein Synthesis and Degradation

As shown in Fig. 23, ribosomes follow the instructions in messenger RNA in order to string together amino acids to form proteins. While the process of choosing which amino acid to add next is rather complicated and will be left for *Molecular Biology and Genetics*, the biochemistry of how amino acids are glued together is rather simple. As illustrated in Fig. 31, the carboxyl terminus or end of an upstream amino acid reacts with the amino terminus of the next downstream amino acid to form a peptide bond plus a leftover water molecule. Doing this process many times with the aid of ribosomes can result in very long proteins with lots of amino acids [Fig. 31(c)]. Different proteins are defined by the types and sequence of their amino acids, or more specifically by all of their side chains.

The reverse process (hydrolysis) is used by protease enzymes to break down proteins into their component amino acids. Some proteases are very picky eaters and will only whack peptide bonds between certain amino acids, and other proteases are more omnivorous and will chew up any amino acid sequence.

To prepare for their new jobs, some proteins require **post-translational modification** in the endoplasmic reticulum and Golgi apparatus. These modifications include glycosylation or adding glycan (sugar) groups, creating disulfide bridges, phosphorylation or adding phosphate groups, and any other modifications required to help the proteins fold up into their final functional form. Figures 32–33 show several examples.

Most proteins must fold up in a specific way to do their particular job. As shown in Figs. 34–35, the structure of a protein is described at different levels: primary (amino acid sequence), secondary (folding of small regions into β-sheet or α-helix structures, tertiary (folded structure of the complete amino acid sequence), and quaternary (assembly of separate monomeric subunits of amino acid sequences to form a complete multimeric protein).

That's all you really need to worry about proteins for right now. Proteins will be covered in much more detail in the fabled, long-awaited *Molecular Biology and Genetics*, sure to be a best-seller.

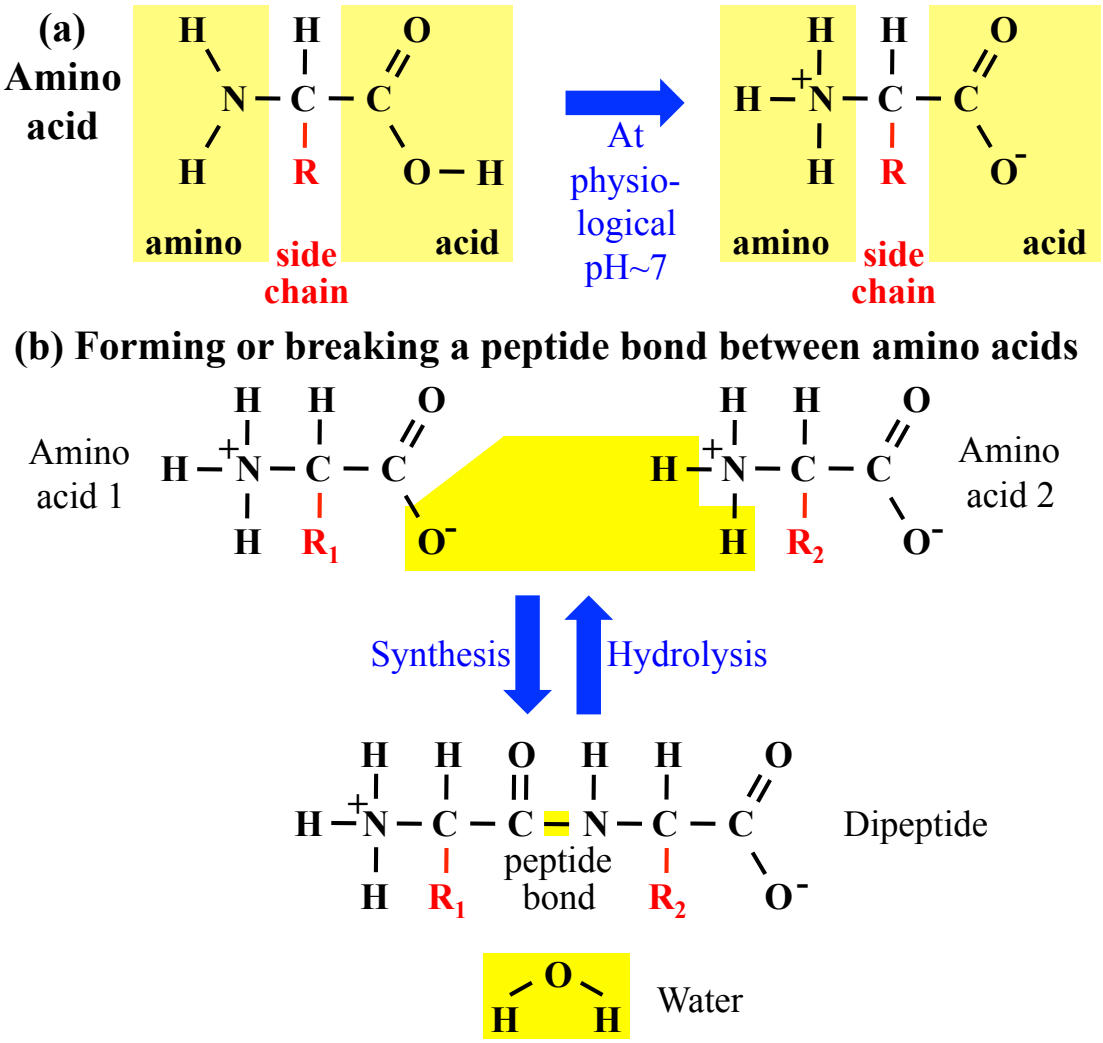


Fig. 31. Protein synthesis from amino acids. **(a)** Amino acids have an amino end that assumes a positive charge under normal physiological conditions, a carboxylic acid end that assumes a negative charge under normal conditions, and a side chain R that could be anything from one to many atoms. **(b)** The carboxyl end of one amino acid can react with the amino end of another amino acid to form a peptide bond between the two plus a leftover water molecule, or that process can be reversed to break the peptide bond. **(c)** Proteins generally have many amino acids, which are defined by the types and sequence of their side chains.

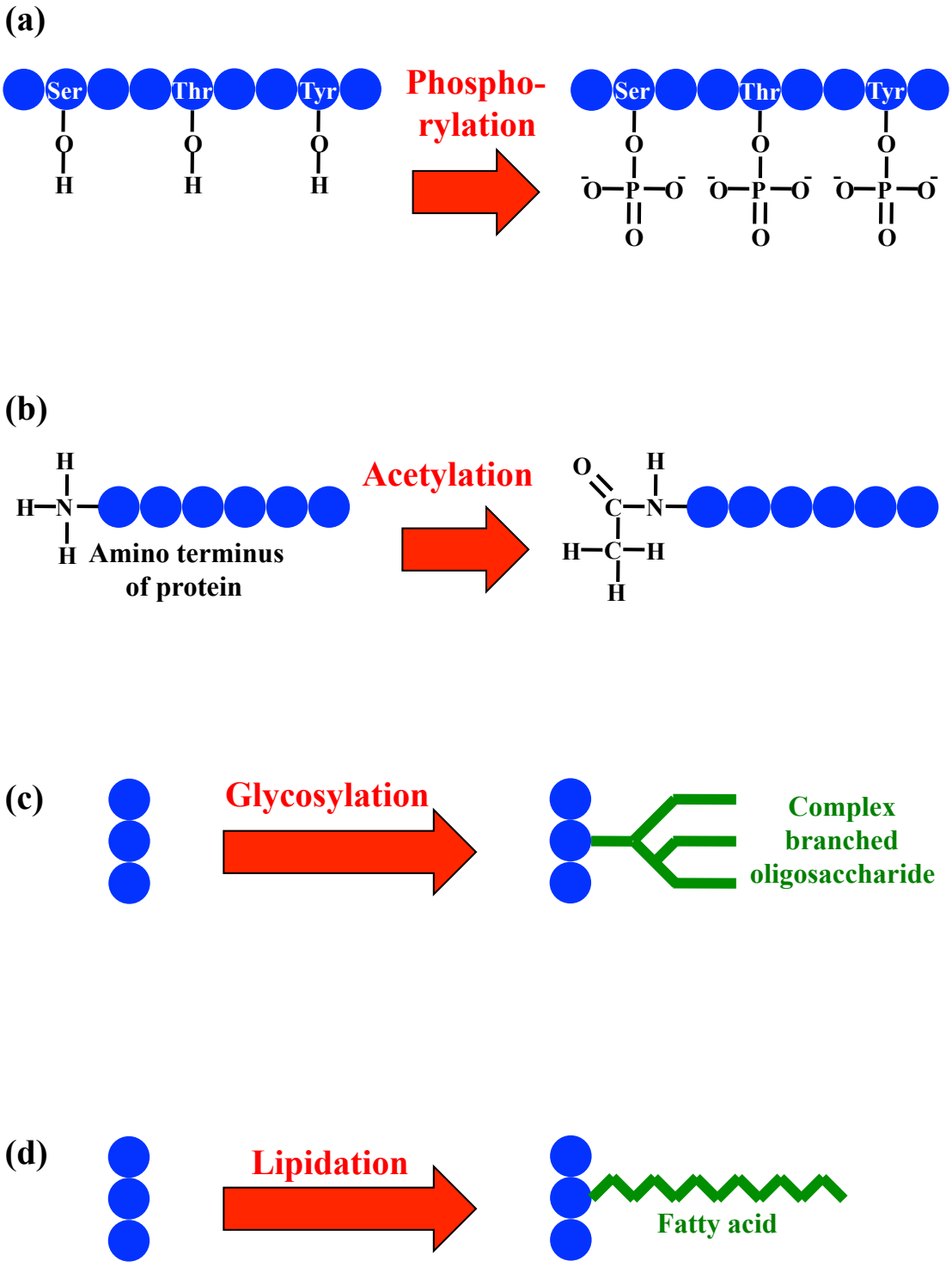


Fig. 32. Some categories of post-translational protein processing include (a) phosphorylation, (b) acetylation, (c) glycosylation, and (d) lipidation.

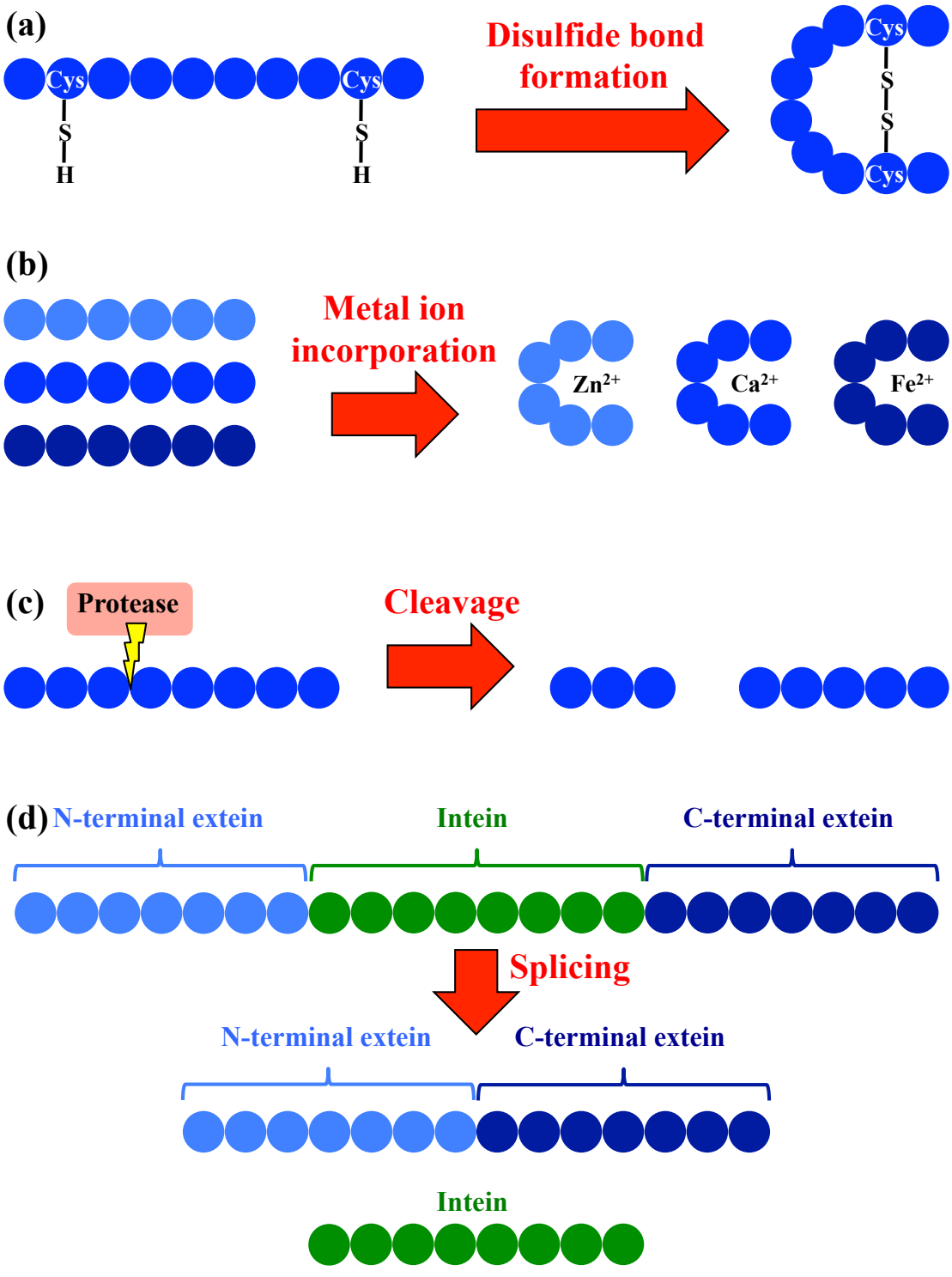


Fig. 33. Additional categories of post-translational protein processing include (a) disulfide bond formation, (b) metal ion incorporation, (c) cleavage, and (d) splicing.

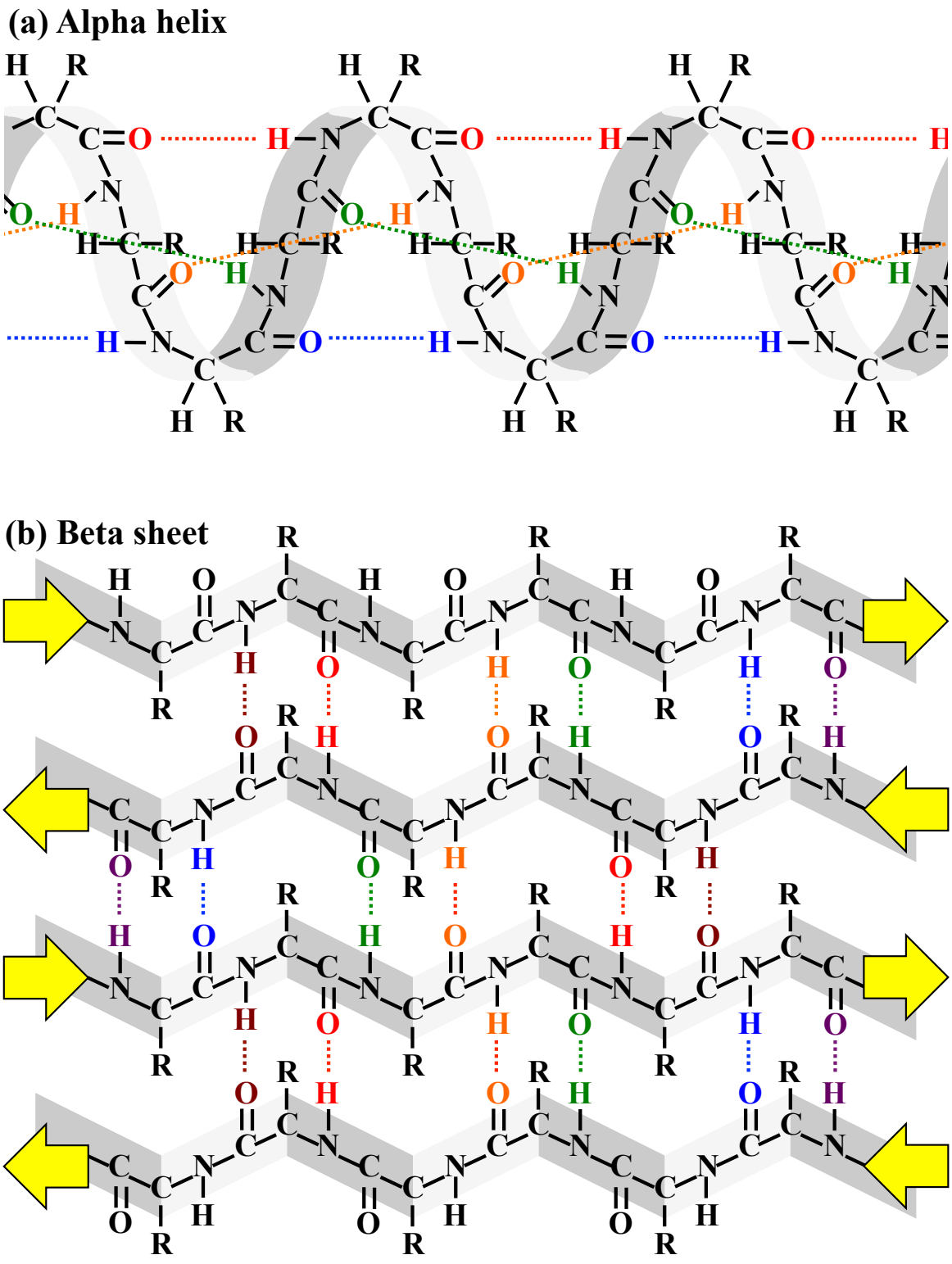


Fig. 34. Protein secondary structure. (a) Alpha helix. (b) Beta sheet.

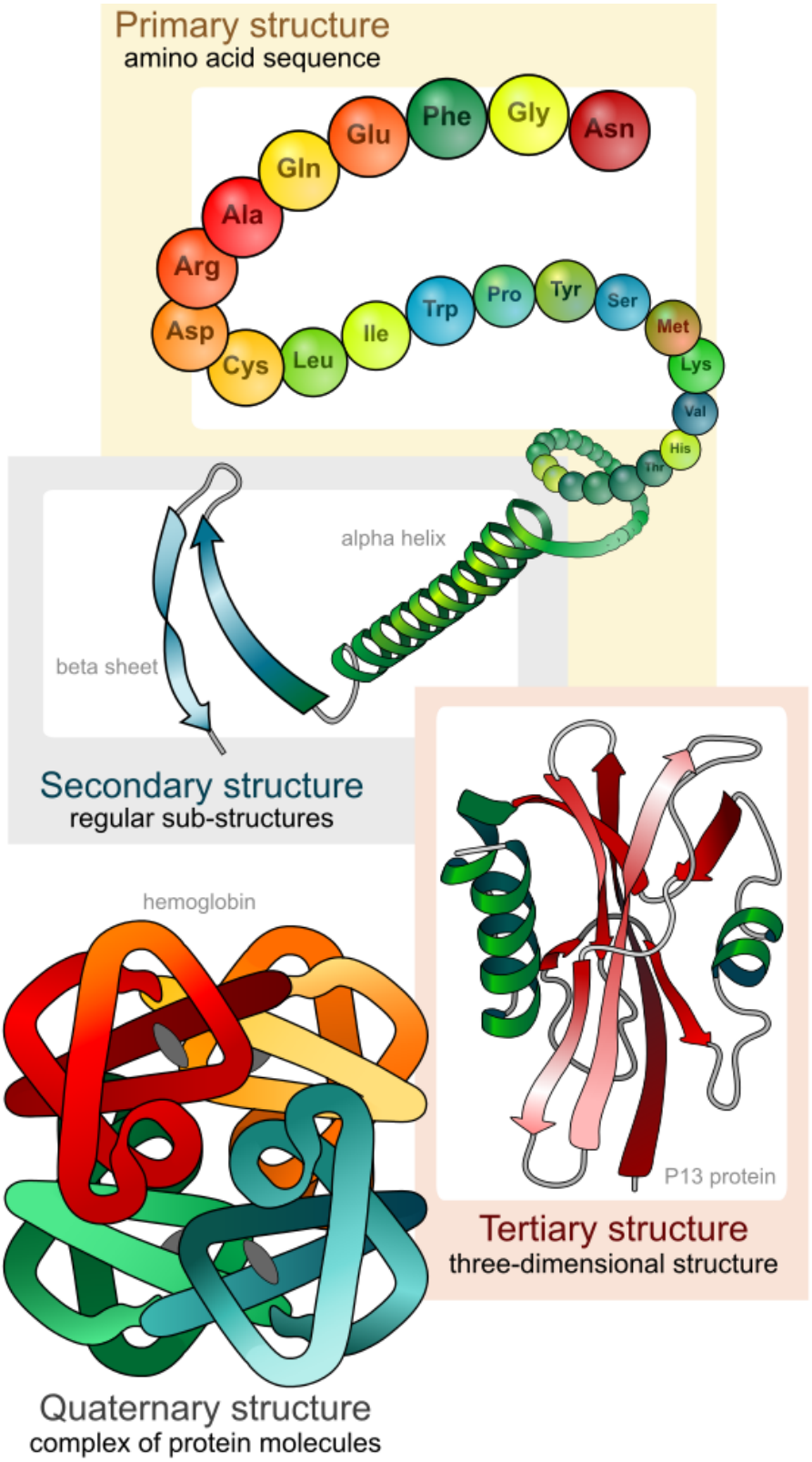


Fig. 35. Protein primary, secondary, tertiary, and quaternary structure (public-domain image from Wikipedia, https://en.wikipedia.org/wiki/Protein_structure).

4 Lipids

Lipid molecules have a bewildering variety of shapes, sizes, and functions. What they all have in common is that most or all of a lipid molecule is very hydrophobic, wanting to avoid electrically polar water molecules. Some of the major categories of lipids are phospholipids, sterols, and fatty acids and triglycerides.

4.1 Phospholipids

The **plasma membrane** surrounds the cell and carefully controls what molecules can enter or leave the cell. Many organelles within cells wanted their own little gated communities and thus are also surrounded by very similar membranes to control what enters and leaves those organelles.

As shown in Fig. 36, membranes are composed of phospholipid molecules. Each phospholipid molecule has a head that is hydrophilic (water-loving), due to its electrically charged and electrically polarized molecular components, and two tails that are hydrophobic or water-avoiding, because they are more neutral than Switzerland. Because of their dualistic nature, phospholipids form bilayer membranes that contain two layers of phospholipids, with the hydrophilic heads facing the water on each side and the hydrophobic tails hiding from the water in the middle of the membrane.

4.2 Sterols

In addition to phosopholipids and proteins, membranes contain other components, including sterols. As shown in Fig. 37, sterols are fairly small lipids that are hydrophobic all the way around, and hence they like to hide somewhere in the middle in membranes. Cells from different critters contain slightly different types of sterols, which can come in handy if you want to kill one type of critters (e.g., a fungal infection) without killing other types of critters (e.g., the human who has the fungal infection). As shown in Fig. 37(b), animal cell membranes contain cholesterol, plant cell membranes contain any of several phytosterols (e.g., stigmasterol), fungal cell membranes contain ergosterol, and bacterial cell membranes contain any of several sterol-like hopanoids (e.g., diploptene).

Cholesterol is also modified in various ways to make steroid hormones, as illustrated in Fig. 38. Different steroid hormones regulate everything from sexual characteristics to blood sugar levels, as will be covered in future summaries on human physiology.

4.3 Fatty Acids and Triglycerides

As shown in Fig. 39, fatty acids are long hydrocarbon chains. Triglycerides are three fatty acids glued to a glycerol group.

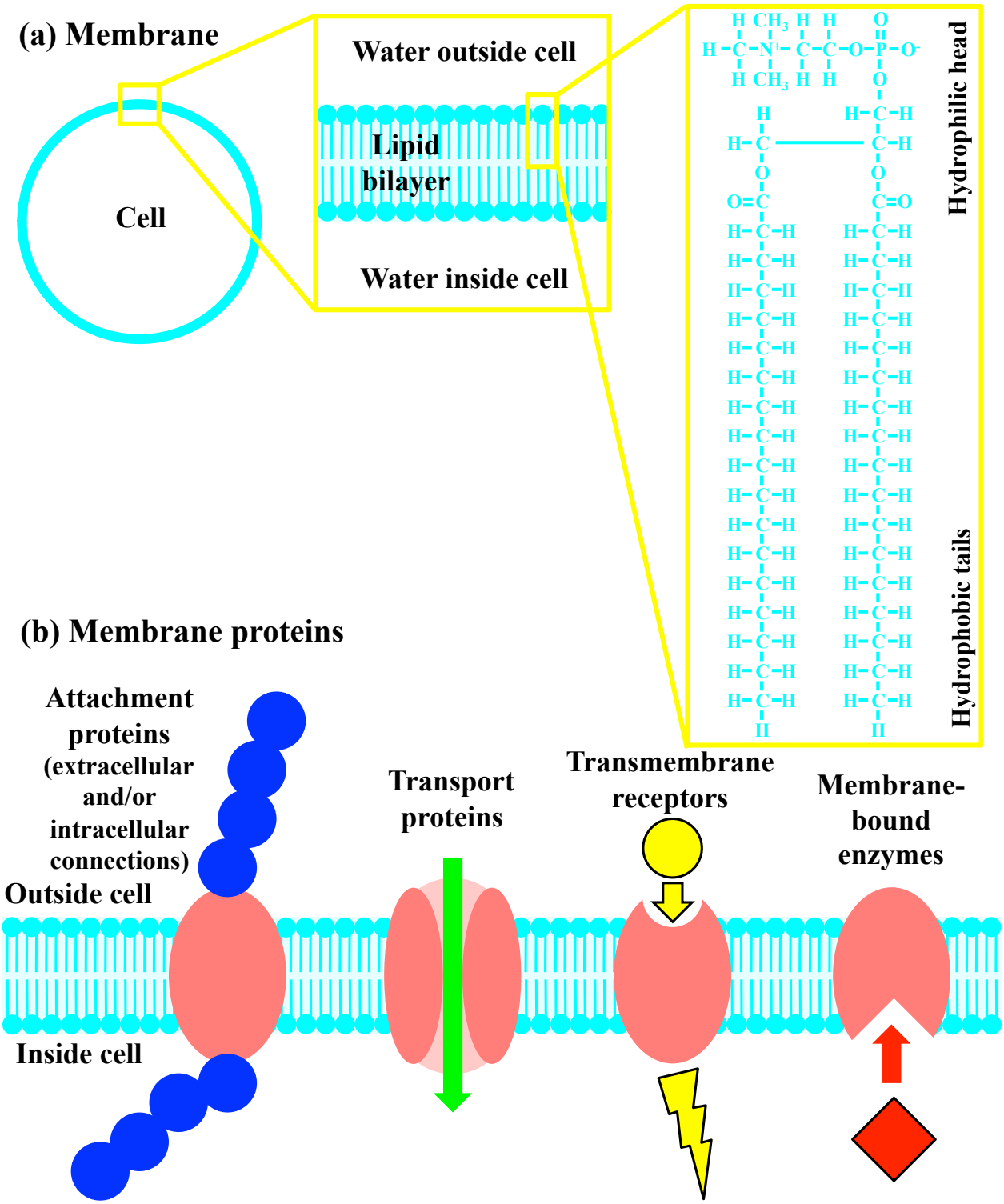


Fig. 36. Cell membrane structure. **(a)** Membranes are made of phospholipid molecules, which have a hydrophilic (water-loving) head and two hydrophobic (water-avoiding) tails, and form two layers, with the hydrophilic heads facing each side and the hydrophobic tails in the middle. **(b)** Membranes contain proteins that attach to extracellular or intracellular connections, transport molecules through the membrane, receive signals, and act as enzymes to catalyze certain reactions.

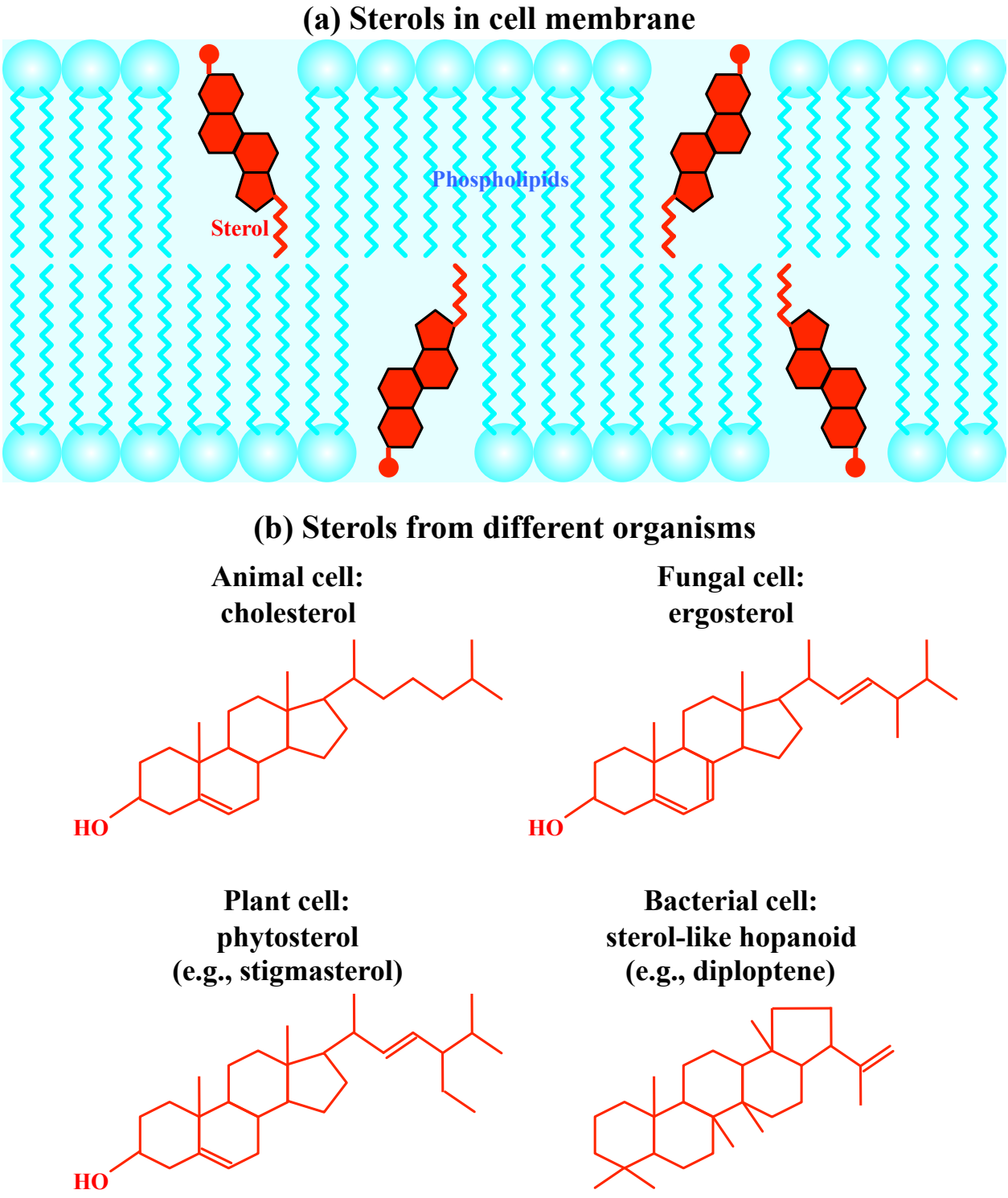


Fig. 37. Membrane sterols. **(a)** Location of sterols in cellular membranes. **(b)** Major types of sterols in membranes from different cell types. (In this compact and widely used notation, unless otherwise indicated, carbon atoms sit where lines end or change directions, and any of the four bonds of each carbon not otherwise used are occupied by hydrogens that are not shown).

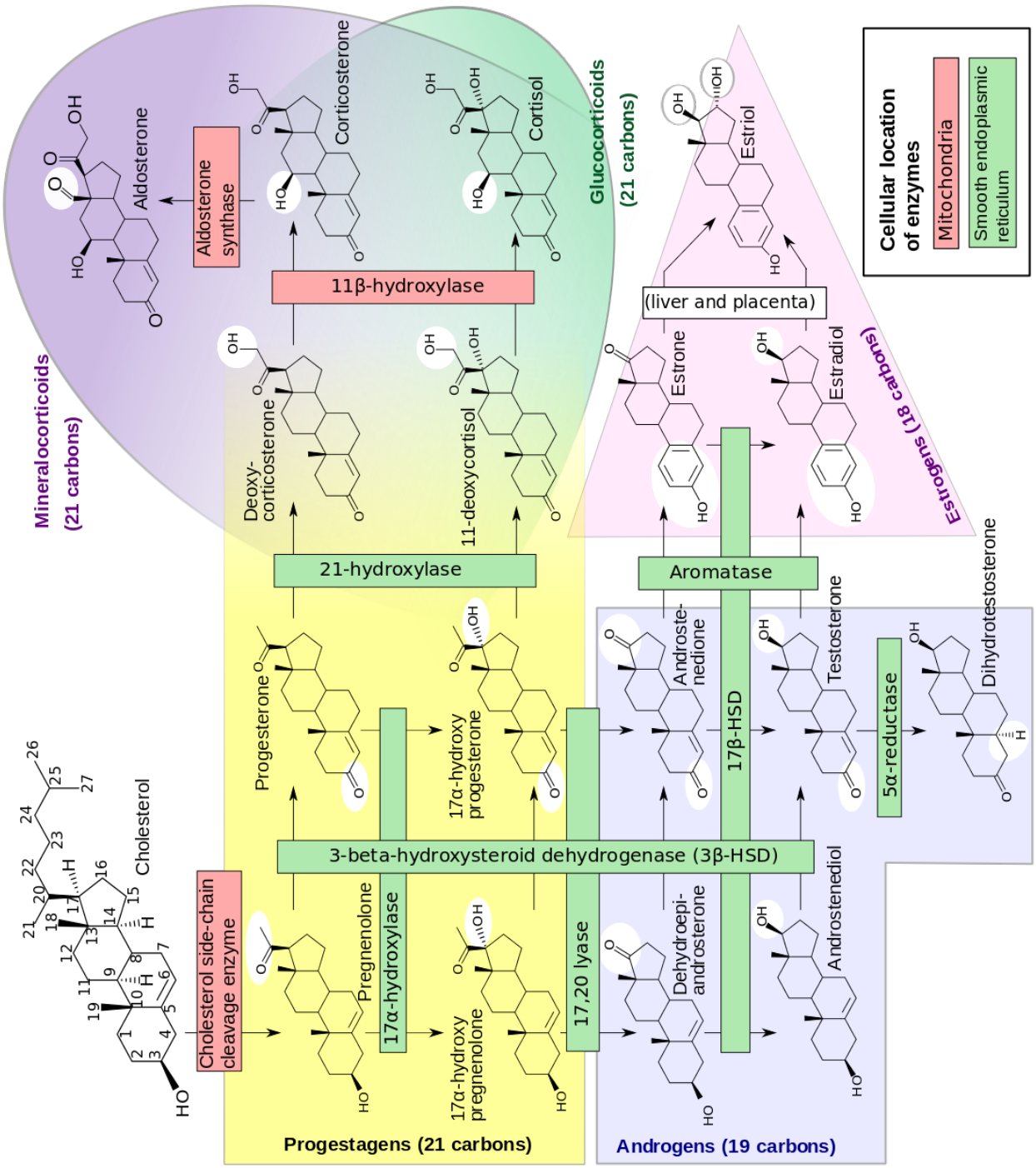


Fig. 38. Steroid hormones. (Image from https://en.wikipedia.org/wiki/Steroid.)

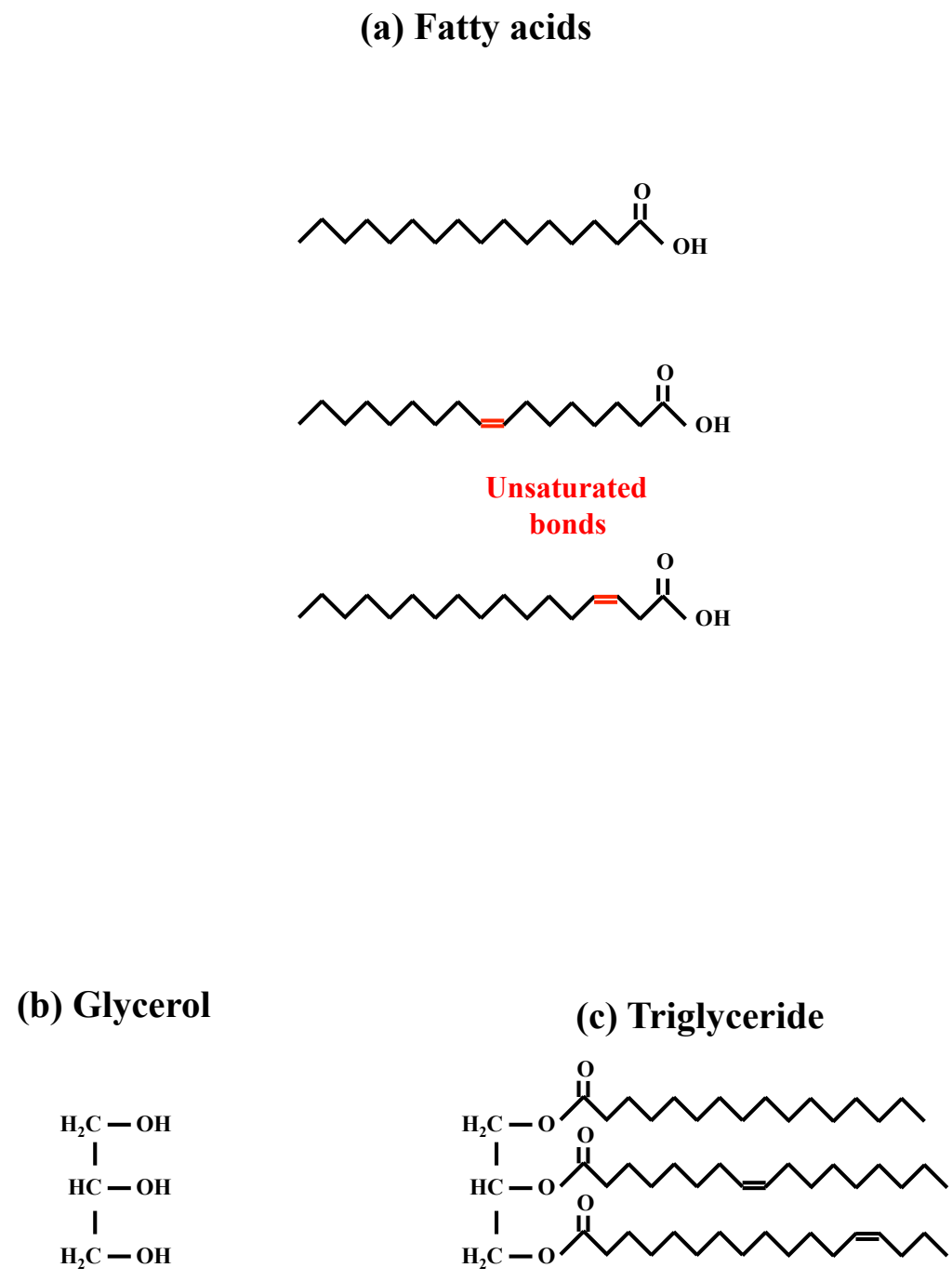


Fig. 39. Fatty acids and triglycerides.

5 Carbohydrates

Carbohydrates are hydrated (H_2O) carbon (C) compounds. They are also called saccharides, because simple carbohydrates are sugars. Each saccharide molecule usually forms a ring. Carbohydrates may be classified as monosaccharides (one sugar or one ring), disaccharides (two sugars or rings glued together), and polysaccharides (more than two sugars or rings glued together, since biologists have never been big on math).

5.1 Monosaccharides

Monosaccharides or simple sugars usually only contain hydrogen (H), oxygen (O), and carbon (C), and like to form a ring of atoms. As shown in Fig. 40(a), some major monosaccharides include:

- **Glucose** ($C_6H_{12}O_6$), called blood sugar since it is the form of sugar that is circulated in the bloodstream to feed all the cells in the body. Cells break glucose in half (pyruvate, Fig. 41), then use the halves to power their mitochondria (Section 7).
- **Galactose** (also $C_6H_{12}O_6$, but note the structure is different than glucose), or milk sugar.
- **Fructose** (again $C_6H_{12}O_6$, but its structure is different than both glucose and fructose) or fruit sugar.
- **Ribose** ($C_5H_{10}O_5$), the form of sugar found in DNA and RNA (**ribo**nucleic acids). Fructose and ribose can be synthesized or degraded via the pentose phosphate pathway in cells (Fig. 42).

5.2 Disaccharides

Disaccharides are two simple sugars clinging to each other for dear life. As shown in Fig. 40(b), some major examples include:

- **Maltose** or grain sugar, two glucoses stuck together.
- **Sucrose** or normal table sugar, one glucose and one fructose glued together.
- **Sucralose**, an artificial sweetener sold as Splenda and other names. Note that it looks exactly like sucrose except chlorine (Cl) atoms replace two hydroxyl (OH) groups. Your taste buds aren't smart enough to tell the difference, but your body cannot figure out how to break it down, so you can have your cake and eat it too.
- **Lactose**, the main form of sugar in milk, one galactose and one glucose hooked together. In your intestines, lactase enzymes split the galactose and glucose apart, and they are separately absorbed into your bloodstream. People who are lactose intolerant do not make the lactase enzyme, so they cannot absorb lactose. That leaves it for the bacteria in your intestines, which have a field day with it and produce lots of gas.
- **Trehalose**, two glucoses glued together in a different way than maltose, which is used as a natural antifreeze in some animals to prevent them from freezing solid in the winter.

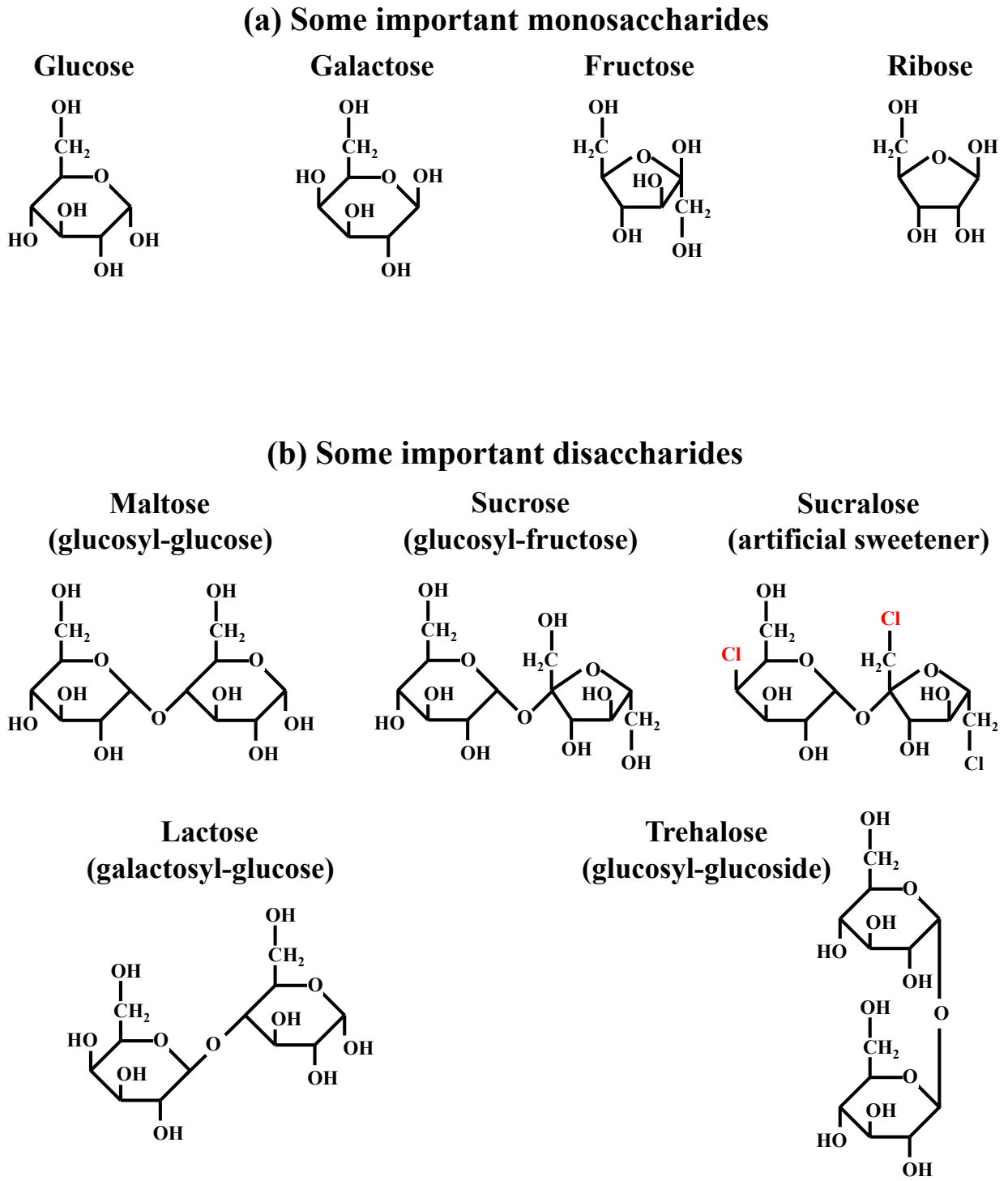


Fig. 40. Some major simple sugars. **(a)** Monosaccharides include glucose, galactose, fructose, and ribose. **(b)** Disaccharides include maltose, sucrose, sucralose (a sucrose-like artificial sweetener), lactose, and trehalose.

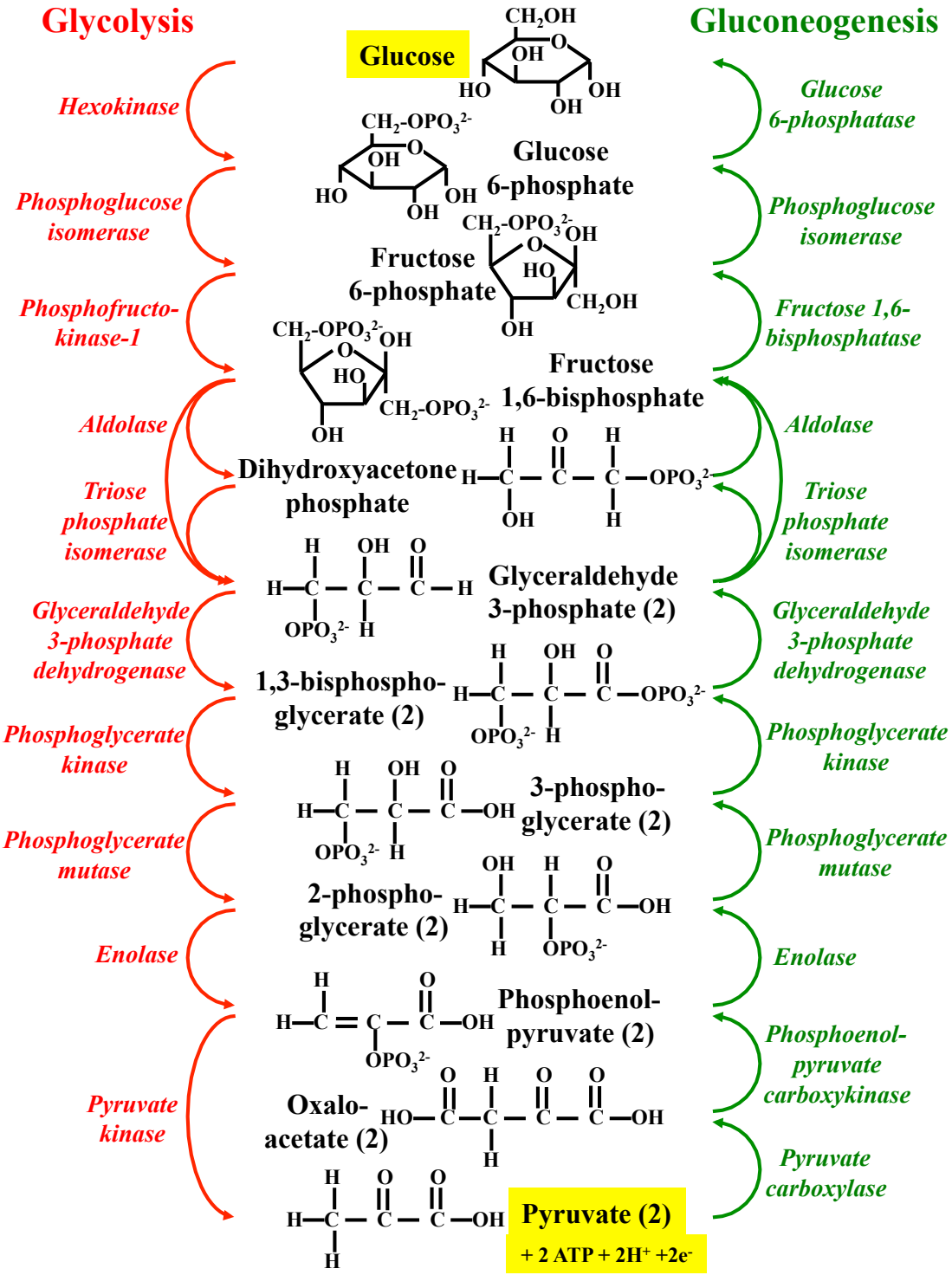


Fig. 41. Glycolysis.

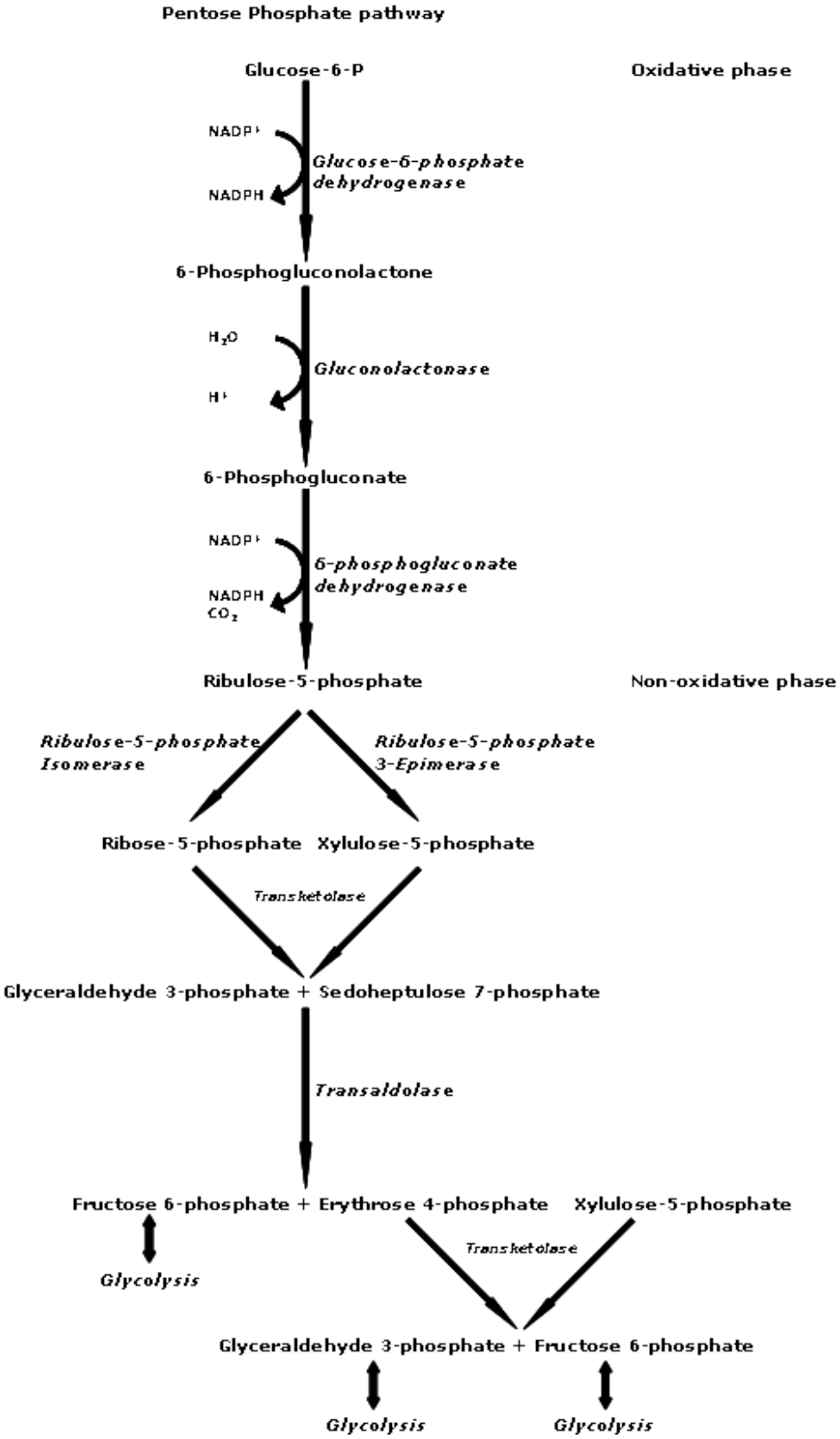


Fig. 42. Pentose phosphate pathway. (From en.wikipedia.org/wiki/Pentose_phosphate_pathway.)

5.3 Polysaccharides

Some major polysaccharides include:

- **Starch**, how plant cells store their extra glucose in case they want a midnight snack later (Fig. 43).

- **Glycogen**, basically the same thing as starch but with more branches, how animal cells store their extra glucose (Figs. 43 and 44).

- **Cellulose**, which forms plant cell walls (Fig. 45). It looks like starch but notice that the glucoses are connected in a slightly different way, which most critters (except the bacteria that live in termites' stomachs) cannot figure out how to digest.

- **Chitin**, which forms the cell walls of fungi and the hard exoskeletons of arthropod (bugs and crustaceans). Notice that it looks like cellulose but with a weird extra chemical group hanging off each glucose, as shown in Fig. 45.

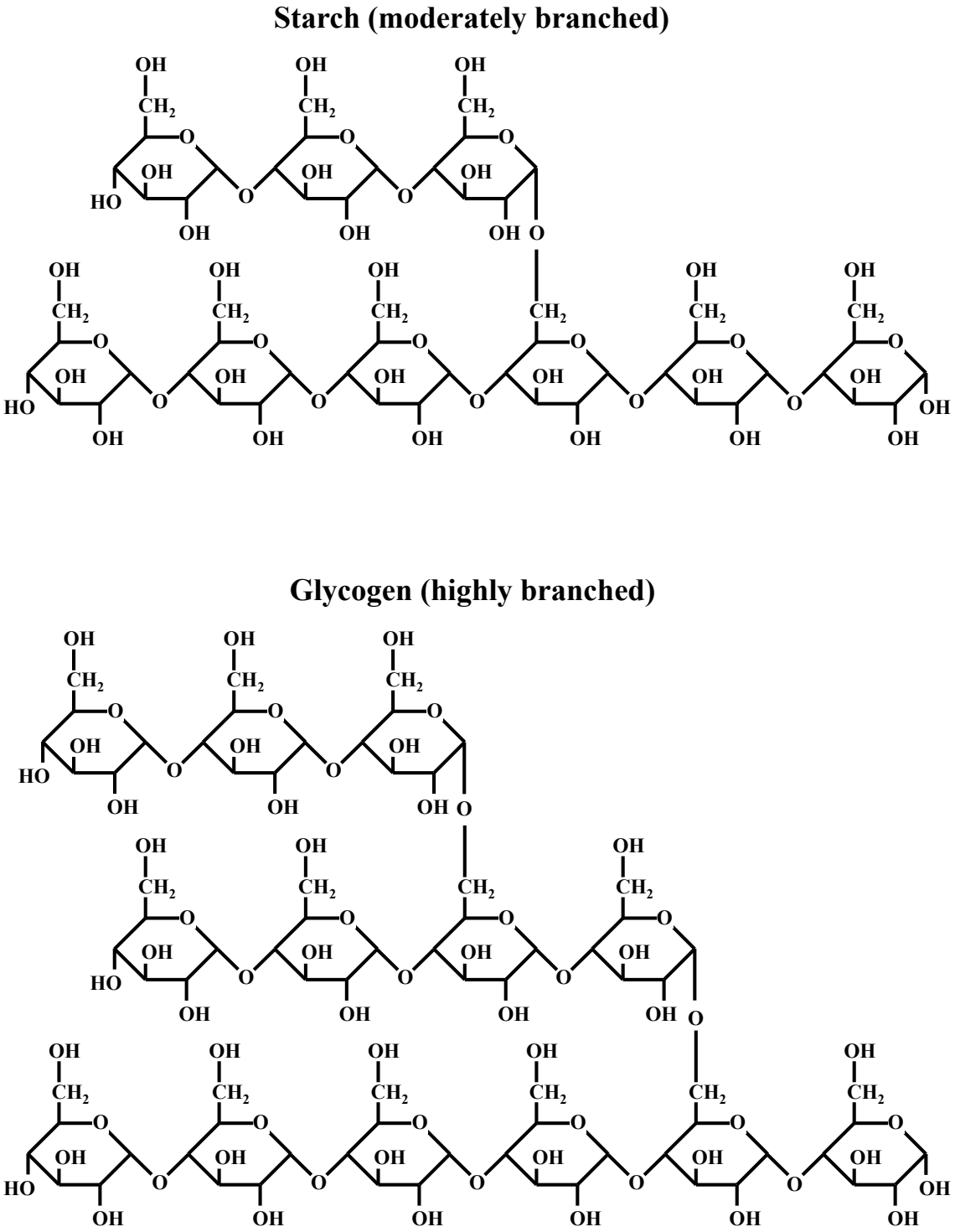


Fig. 43. Structures of starch and glycogen.

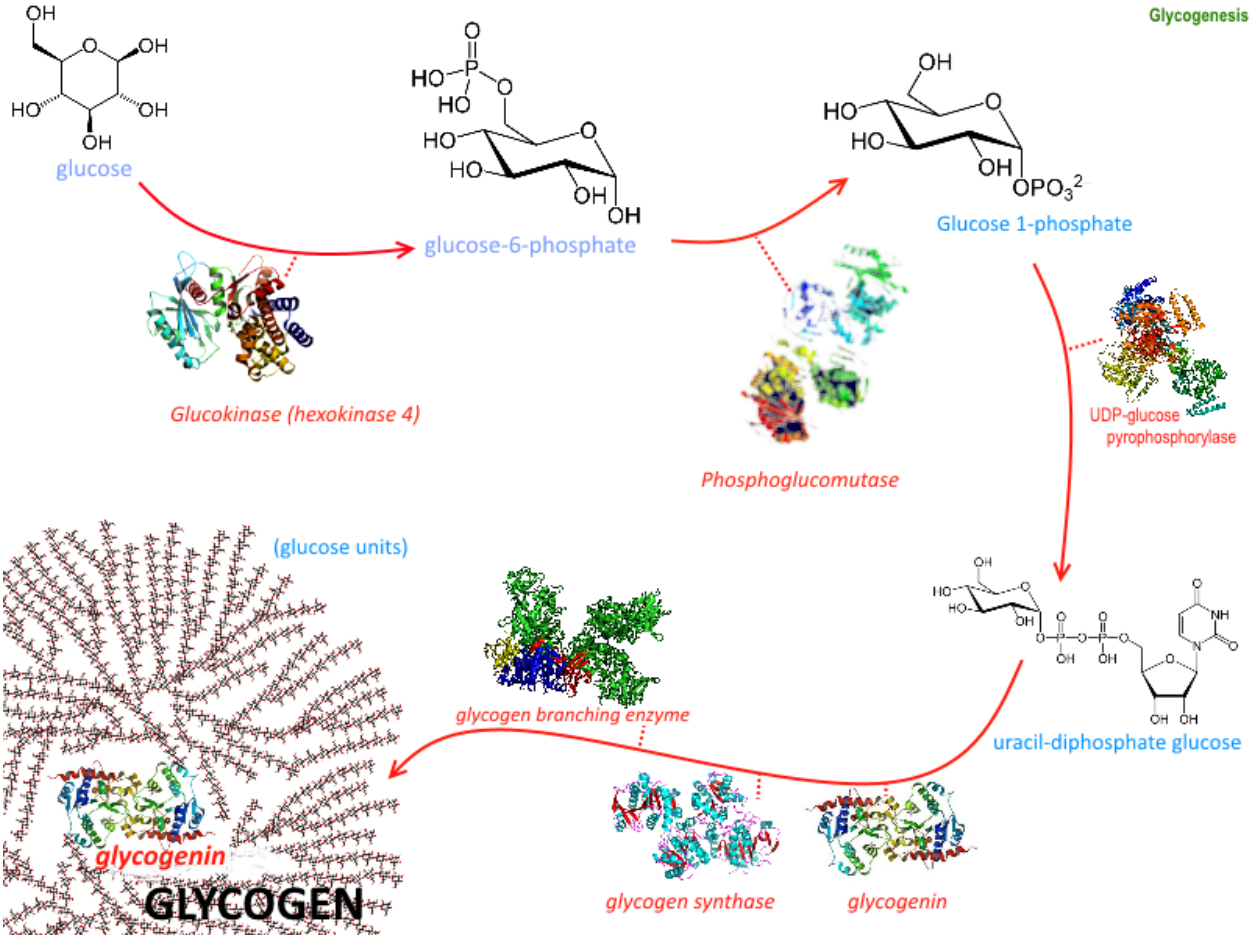


Fig. 44. Glycogen synthesis. (Image from https://en.wikipedia.org/wiki/Glycogenesis.)

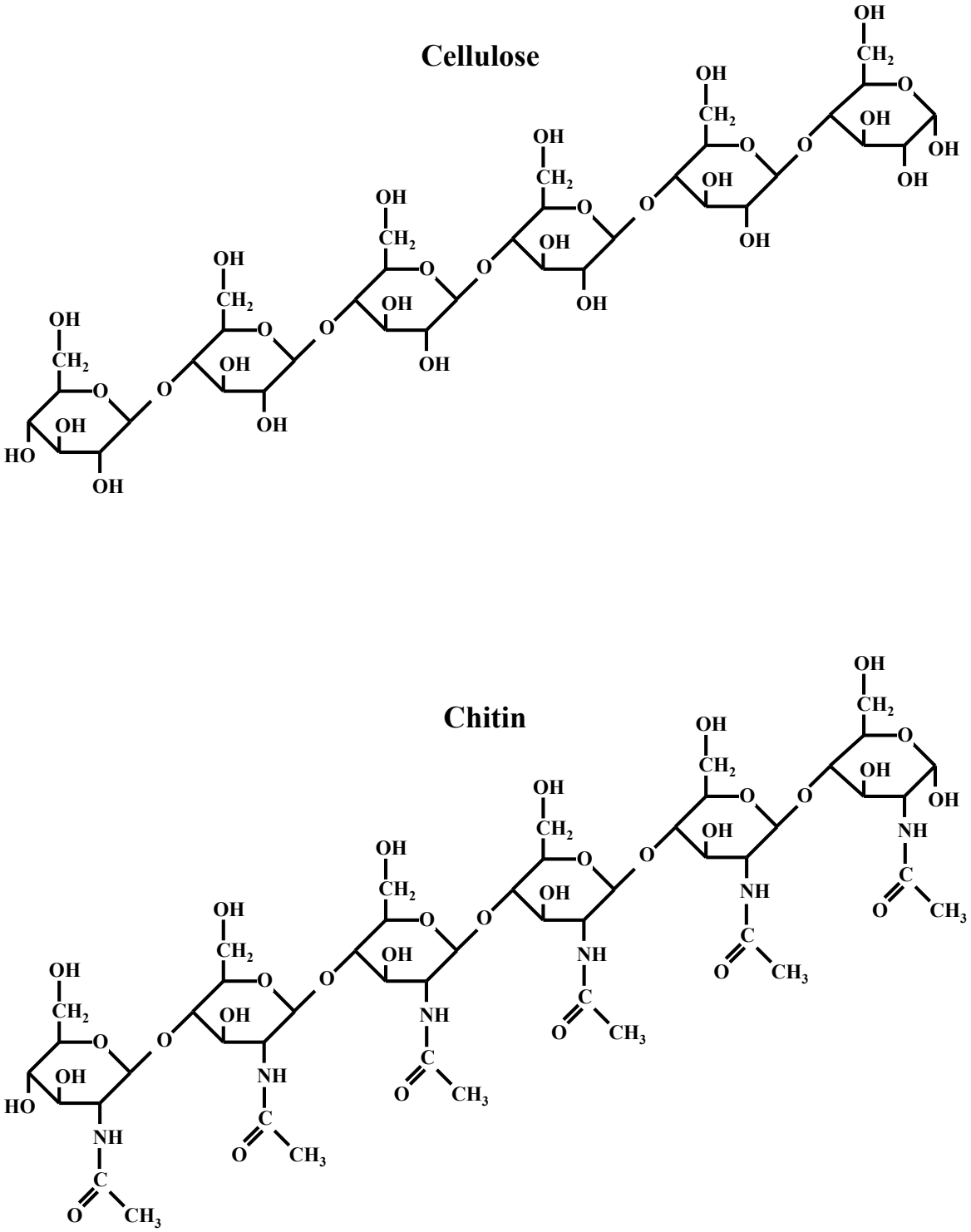


Fig. 45. Structures of cellulose and chitin.

6 Porphyrins

Porphyrins are flower-shaped molecules with a metal ion at their center, as illustrated in Fig. 46. Heme and heme-related porphyrins have an iron (Fe) ion at the center, whereas chlorophylls and closely related porphyrins have a magnesium (Mg) ion at the center. Porphyrins show up in many locations and roles, but their general purpose is to help convert one form of energy into another, for example by transporting oxygen in the blood (heme-containing hemoglobin) to power cells throughout the body, controlling energetic reactions that consume or produce oxygen (heme-containing cytochromes), and absorbing light energy in plants (chlorophyll). Different conditions make porphyrins turn lots of different colors like mood rings, from green in plant chlorophyll to red in oxygen-rich blood hemoglobin to blue in oxygen-deprived hemoglobin to yellow in bilirubin.

6.1 Heme

Porphyrins are very complicated flower-shaped molecules that cells have to build from scratch. As shown in Fig. 47, cells start with basic components such as glycine amino acids and succinyl-CoA from the citric acid cycle (Section 8.2), go through a gazillion steps (you're welcome for not getting dragged through them here), and end up with protoporphyrin IX, which has all the bells and whistles except a metal ion.

As shown in Fig. 47, if iron (Fe) is added to the center of protoporphyrin IX, it becomes heme B. (You were expecting protoporphyrin X?) The heme molecule can then be added to different proteins to form complete hemoglobin, myoglobin, cytochromes, enzymes, etc.

When those heme-associated proteins reach the end of their careers, the heme is detached from the proteins. The proteins are broken down like other proteins, but heme is powerful stuff and requires special disposal methods. First the iron is removed, and then the flower-shaped ring is broken in one place (Fig. 47 lower left). This heme breakdown product is called bilirubin and is yellow and toxic. It is transported out of cells through the bloodstream and removed by the kidneys, which is why urine is yellow. Some of it is also excreted in feces. Newborne babies have bright yellow poop due to the bilirubin. The rest of us have brown poop since nonpathogenic bacteria have taken up residence in our intestine and oxidize the bilirubin to a brown color. Too much information!

Malaria is an infectious disease caused by *Plasmodium* protozoa, which are transmitted by mosquito bites, enter red blood cells, and eat the red blood cells from inside out like the world's tiniest vampires (*Microbiology* section 6). Specifically, they digest the hemoglobin inside red blood cells to toxic heme waste products and gain some energy in the process. To avoid poisoning themselves with their own toxic heme waste, the protozoa convert toxic individual heme molecules into nontoxic hemozoin crystals or clumps that precipate out of solution (Fig. 47 lower right). Most of the major drugs for malaria (quinine, chloroquine, mefloquine, primaquine, etc.) bind to individual heme molecules and prevent formation of hemozoin clumps. Thus the protozoa end up getting killed inside red blood cells by their own toxic heme waste that they can no longer eliminate.

Although heme B is the major type of heme, there are two other types, which are logically called heme A and heme C. As shown in Fig. 48, the different types of heme differ in what is attached to the outer edge of the flower shape.

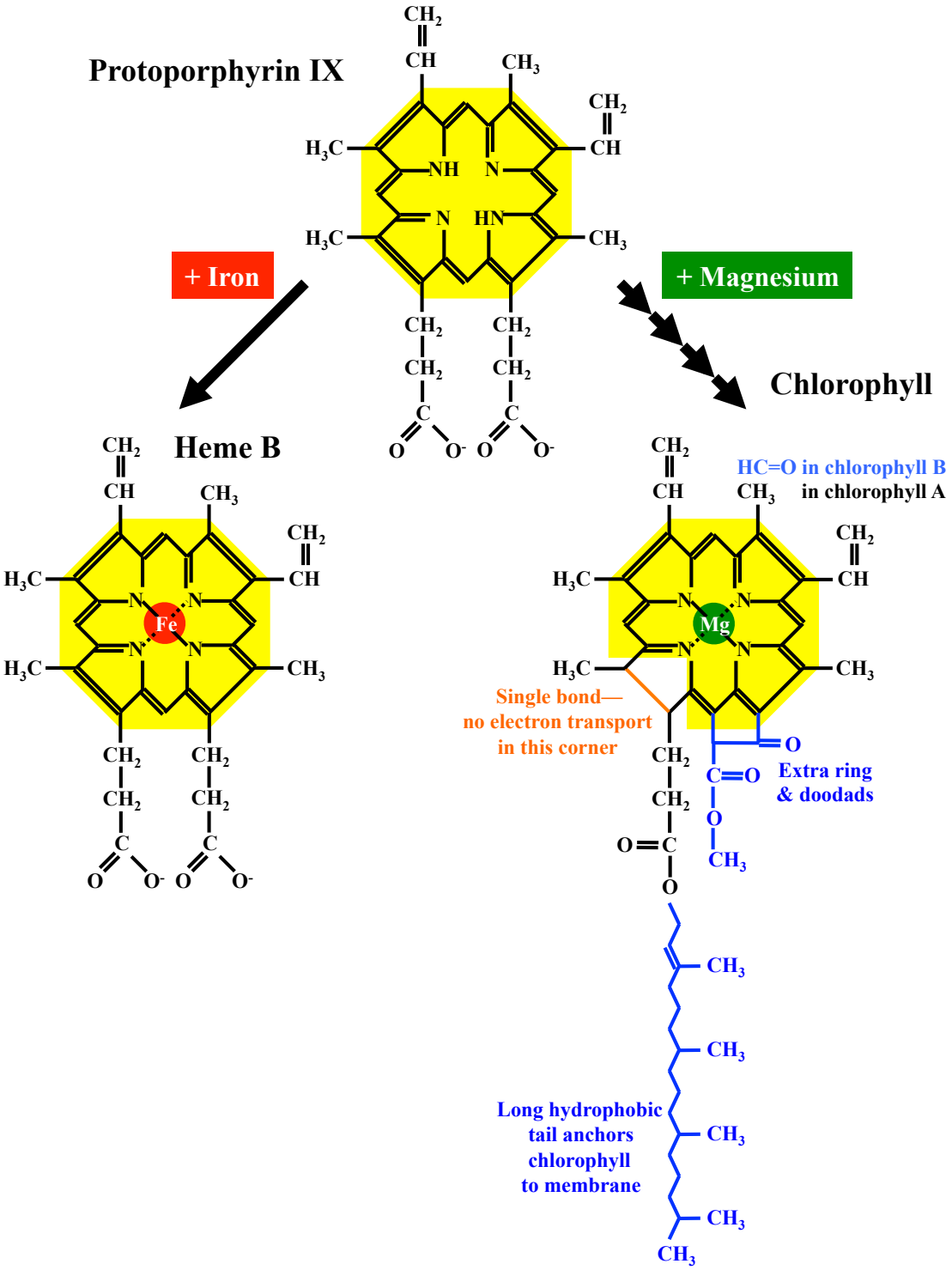


Fig. 46. Synthesis of chlorophyll vs. heme.

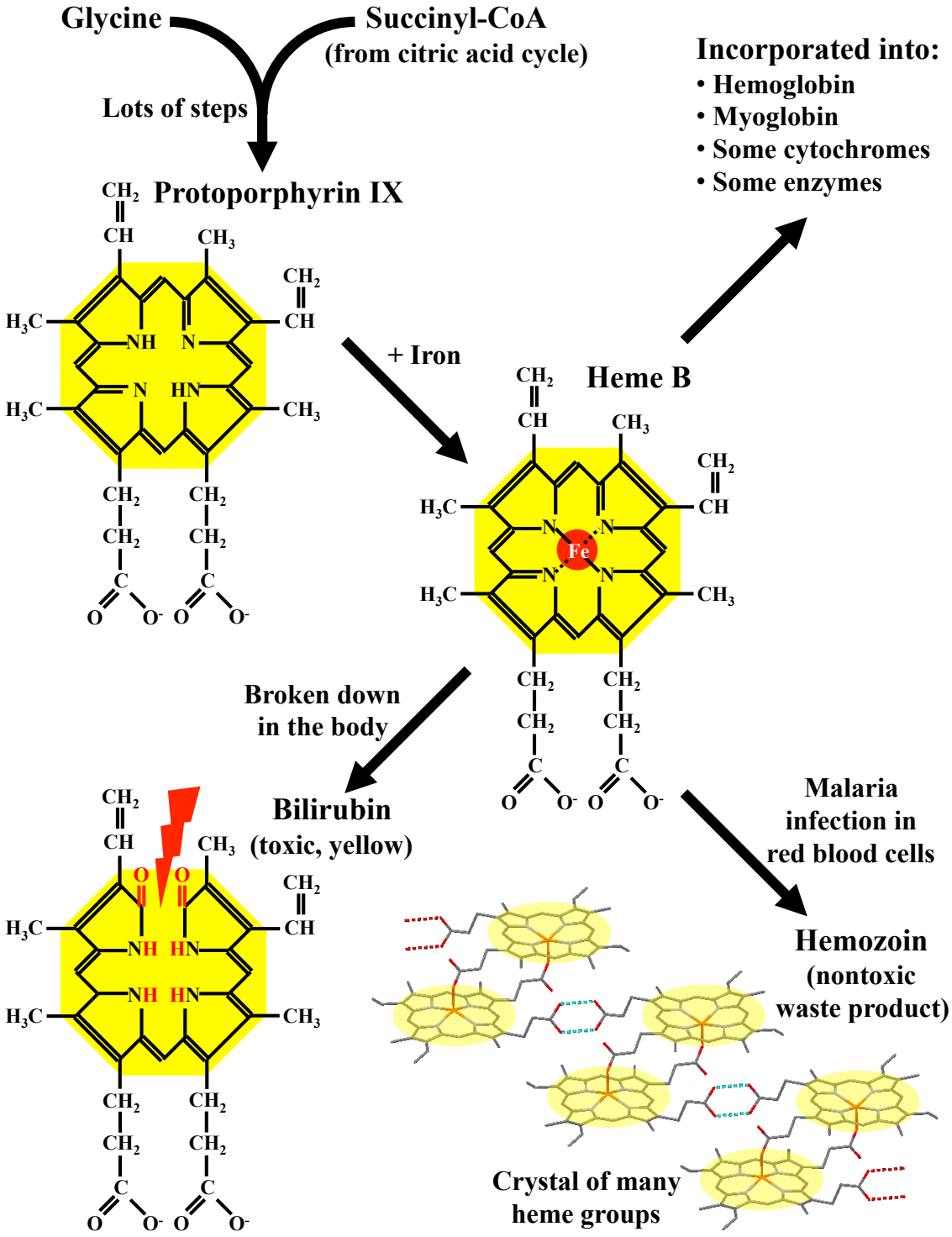


Fig. 47. Synthesis and degradation of heme.

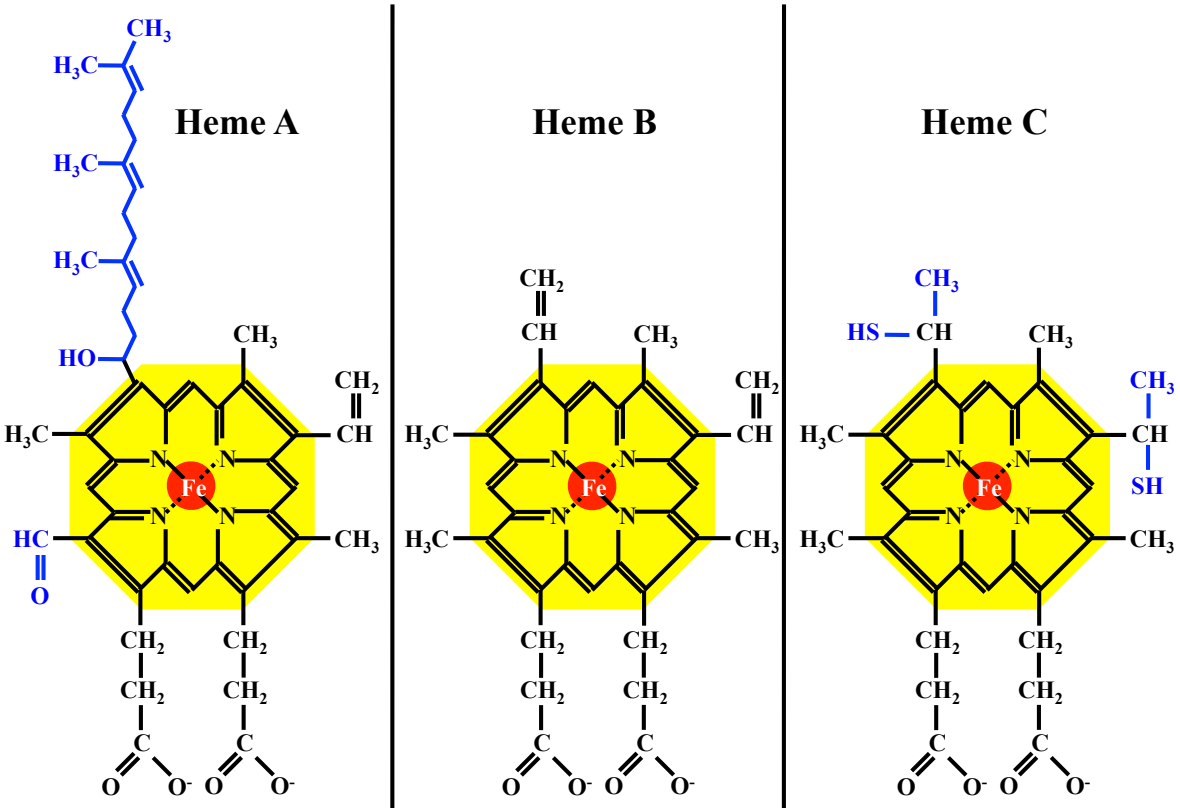


Fig. 48. Heme types A, B, and C.

Heme A is incorporated into:

- Cytochromes type a, which play key roles in electron transport and energy conversion in mitochondria (Section 8.2) and bacteria.
- Cytochrome c oxidase, which also plays important roles in electron transport and energy conversion in mitochondria (Section 8.2) and bacteria.

Heme B is incorporated into:

- Hemoglobin, the oxygen-binding protein in red blood cells.
- Myoglobin, an oxygen-binding protein in muscles.
- Cytochromes type b, which play key roles in electron transport and energy conversion in mitochondria (Section 8.2), chloroplasts (Section 10.2), and bacteria.
- Cytochromes P450, which are especially imporant in liver metabolism.
- Catalase, an enzyme that catalyzes the decomposition of damaging hydrogen peroxide (H_2O_2) to normal water and oxygen.
- Peroxidases, enzymes that catalyze the conversion of other dangerous free oxygen radical molecules to safer molecules.
- Nitric oxide synthases, enzymes that produce nitric oxide (NO) molecules as a method of cellular signaling.
- Other enzymes, such as cyclooxygenase enzymes that are involved in inflammatory pathway signaling.

Heme C is incorporated into:

- Cytochromes type c, which play important roles in electron transport and energy conversion in mitochondria (Section 8.2) and bacteria.

6.2 Chlorophyll

As illustrated in Fig. 46, chlorophyll is very similar to heme, except chlorophyll has a magnesium ion at its center whereas heme has an iron ion there. Chlorophyll also has a few other structural modifications compared to heme:

- A single bond instead of a double bond, as shown in orange on the lower left side of chlorophyll. Having alternating double and single bonds in the rest of the porphyrin flower shape allows electrons to move freely, with double bonds becoming single bonds and single bonds becoming double bonds, then back again. Compared to heme, chlorophyll has no electron transport in its lower left corner due to the orange single bond with single bonds on either side of it.
- A long hydrophobic tail that anchors chlorophyll to thylakoid membranes inside plant chloroplasts, as shown in blue on the lower left side of chlorophyll.
- An extra ring and other connected doodads, as shown in blue on the lower right side of chlorophyll.
- A black methyl (CH_3) group on the upper right side of chlorophyll A, just like heme, but a blue HC=O group in that position in chlorophyll B.

7 Vitamins

Vitamins are assorted strange-looking biomolecules that the human body needs but is unable to make. Fortunately, they are made by plants, fungi, bacteria, or other critters and work their way up the food chain until they get to us. If you don't have the patience to wait for that, a wide variety of foods in developed countries are fortified (artificially spiked) with extra vitamins. Or if you are still afraid of being left out, plenty of companies are happy to sell you a bottle of pills. The structures of vitamins don't have much in common with each other, except that they don't really fall into the other categories of biomolecules we have discussed so far, so we have unceremoniously dumped them all into a holding cell here. Vitamins may be divided into those that are hydrophobic and therefore fat-soluble, and those that are hydrophilic and therefore water-soluble.

7.1 Fat-Soluble Vitamins

Some vitamins are hydrophobic, or readily soluble in fat but not water. We might classify these vitamins as lipids, except unlike the lipids discussed in Section 4, the human body cannot make these. Because fat-soluble vitamins can accumulate in body fat and are difficult to dissolve in water and eliminate in urine, they can last a long time (that's the good news) but can have toxic effects if they are consumed in excess (that's the bad news). As shown in Fig. 49, some major fat-soluble vitamins include:

- **Vitamin A (retinol)** or its chemical precursors like β-carotene (two retinols glued together) can be derived from certain plants such as carrots, sweet potato, pumpkin, spinach, kale, etc., or fats from animals that have previously ingested such plants. Retinol and its related forms retinal and retinoic acid are essential components of light-detecting rhodopsin molecules in the eye and of some DNA-regulating transcription factors in cell nuclei. Lack of dietary vitamin A can cause blindness and sterility. Excessive vitamin A can cause liver damage or birth defects. You're already getting stressed out about vitamins, right?

- **Vitamin D (cholecalciferol)** can be made from cholesterol in human skin cells that are exposed to enough sunlight. For nerds who don't like sunlight, cholecalciferol or chemically related forms such as ergocalciferol can be derived from certain mushrooms, alfalfa, fats or eggs from animals that have previously ingested such foods, or milk that has been artificially spiked with vitamin D. Vitamin D acts on the intestine and bones to maintain sufficient levels of calcium and phosphorus in the body. Insufficient vitamin D can cause bone demineralization and deformation (called **rickets** in children or **osteomalacia** in adults). Very high levels of vitamin D can cause nausea or kidney stones.

- **Vitamin E (tocopherol)** is found in vegetable oils (canola oil, palm oil, olive oil, etc.), but those are used to make lots of foods, so we should be okay. Vitamin E acts as an antioxidant to prevent oxidative damage to cells by free oxygen radicals (molecules containing very chemically reactive oxygens, not little wild-haired guys shouting to "free the oxygens"). Too little vitamin E can increase oxidative damage in cells, especially red blood cells that carry lots of oxygen and neurons that use lots of oxygen. Very high levels of vitamin E can act as an anticoagulant to interfere with proper blood clotting.

- **Vitamin K (phylloquinone)** can be derived from disgusting leafy green vegetables such as spinach, collard greens, broccoli, and Brussels sprouts. If you don't want to eat those, that's okay–vitamin K is also made by the handy bacteria that naturally live inside your gastrointestinal tract. Vitamin K is used as a coenzyme to modify a number of human proteins, most of which play key roles in blood clotting. Too little vitamin K can hinder blood clotting, and too much can potentially harm red blood cells.

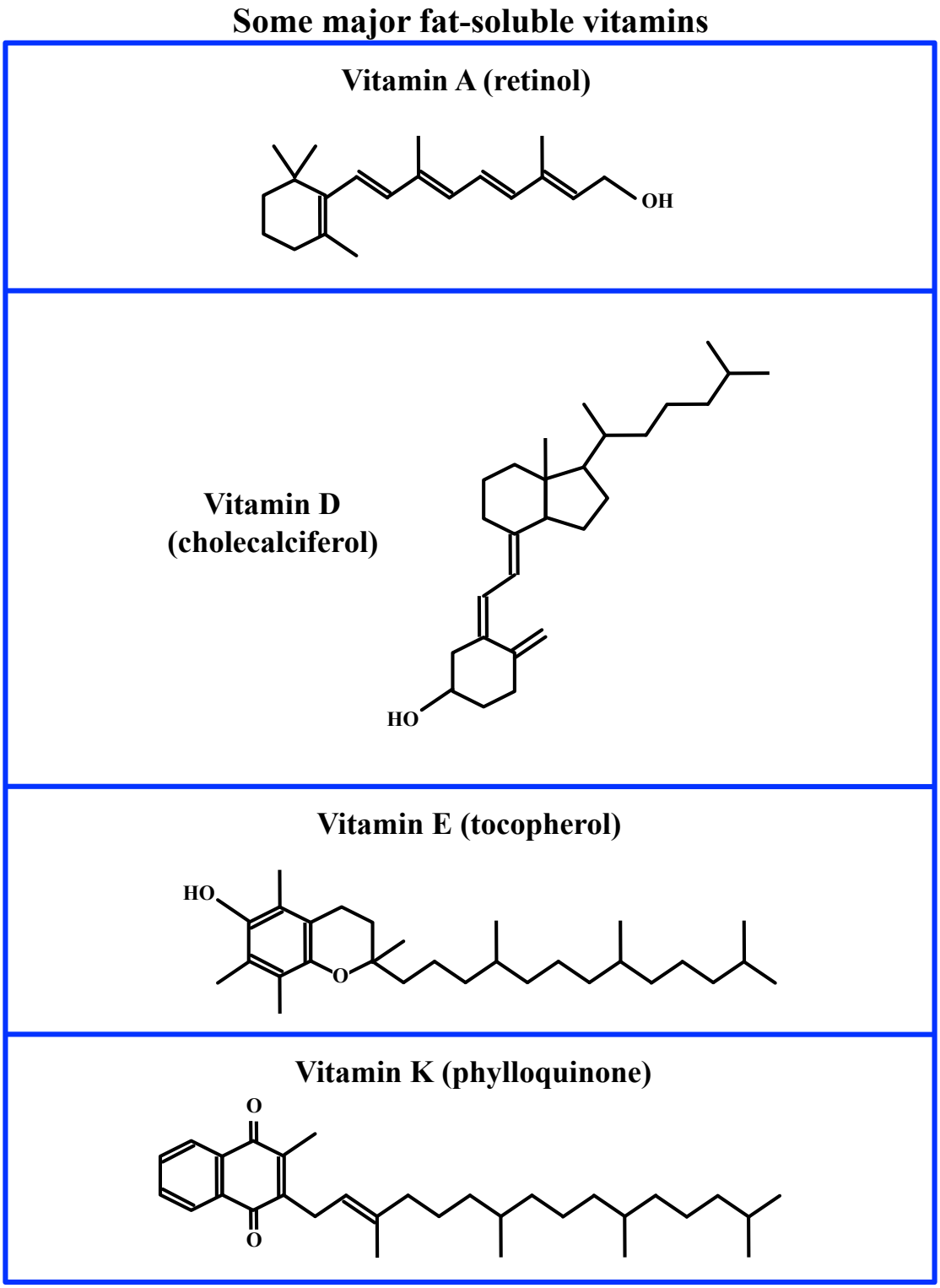


Fig. 49. Some major fat-soluble vitamins include: vitamin A (retinol), vitamin D (cholecalciferol), vitamin E (tocopherol), and vitamin K (phylloquinone).

7.2 Water-Soluble Vitamins

Other vitamins are hydrophilic, or readily soluble in water but not fat. Thus they are not stored in body fat and are readily eliminated in urine. As a result, the bad news is that one can quickly become deficient in these vitamins if they are not consumed regularly, and the good news is that it is difficult to overdose on them.

In general, these water-soluble vitamins are essential for:

1. **Synthesis of biomolecules** such as amino acids and nucleotides, and/or

2. **Metabolism to produce energy** by breaking down fats and sugars.

Therefore, the effects of water-soluble vitamin deficiencies are most pronounced in:

1. **Rapidly-dividing cells** that need lots of biomolecular synthesis and energetic metabolism, such as blood-cell-producing bone marrow, mucous membrane and skin cells, and developing embryos.

2. **Neurons** in the central or peripheral nervous system that are damaged if their steady energetic metabolism is interrupted.

As shown in Figs. 50–51, some major water-soluble vitamins include:

- **Vitamin B_1 (thiamine)** can be derived from whole grains, legumes, nuts, or fungi, or from products (e.g., animal liver or chicken eggs) from animals that have consumed those foods. It is a precursor for thiamine pyrophosphate (TPP), a coenzyme essential for preparing sugars for the energy-producing citric acid cycle (Section 8.2). Thiamine deficiency can damage the central nervous system, which is most dependent on consistent energy production from sugars; this condition is called **beriberi** and manifests as tingling sensations, poor coordination, heartbeat irregularities, and a propensity to make up funny names for vitamin deficiencies.

- **Vitamin B_2 (riboflavin)** is found in leafy vegetables, legumes, and products (milk, eggs, liver) from animals that have consumed those foods. If cells add a phosphate to riboflavin, it becomes flavin mononucleotide (FMN or $FMNH_2$). If cells glue an adenosine diphosphate (ADP) to riboflavin, it becomes flavin adenine dinucleotide (FAD or $FADH_2$, shown in Fig. 17). FMN and FAD are major electron and proton transport proteins. Riboflavin deficiency can cause anemia and inflammation of mucous membranes, but a wide variety of processed food ingredients in developed countries are fortified with extra riboflavin.

- **Vitamin B_3 (niacin)** can be derived from grains, cereal, nuts, milk, and meat. It is an essential precursor of nicotinamide adenine dinucleotide (NAD^+ or NADH) and nicotinamide adenine dinucleotide phosphate ($NADP^+$ or NADPH), two major electron and proton transport proteins shown in Fig. 16. Niacin deficiency can cause mental confusion and damage to the skin and gastrointestinal membranes.

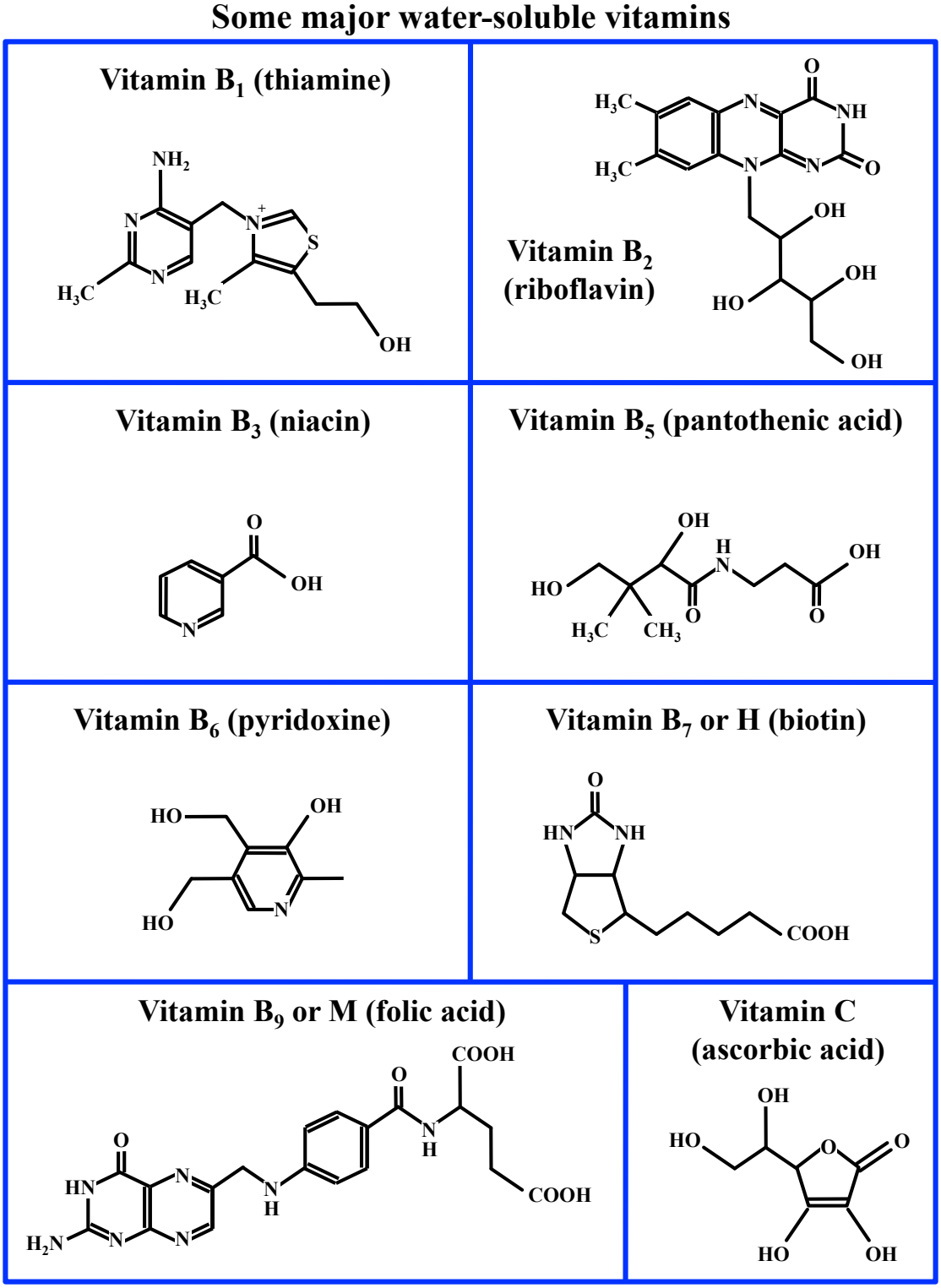


Fig. 50. Some major water-soluble vitamins include: vitamin B_1 (thiamine), vitamin B_2 (riboflavin), vitamin B_3 (niacin), vitamin B_5 (pantothenic acid), vitamin B_6 (pyridoxine), vitamin B_7 or H (biotin), vitamin B_9 or M (folic acid), vitamin C (ascorbic acid), and vitamin B_{12} (cobalamin, Fig. 51).

- **Vitamin B_5 (pantothenic acid)** is found in a very wide variety of plant- and animal-derived foods and is a component of coenzyme A (CoA), which carries several molecules through metabolic pathways. Because pantothenic acid is so widespread, its deficiency is very uncommon except in cases of starvation, where its absence from the metabolic pathways appears to exacerbate the lack of energy production and cause loss of sensation in the skin.

- **Vitamin B_6 (pyridoxine)** is also found in a very wide variety of plant- and animal-derived foods, and it is a precursor of pyridoxal 5'-phosphate (PLP), a cofactor for a number of metabolic reactions. Insufficient pyridoxine can cause dermatitis, anemia, and central nervous system impairment (irritability, convulsions, and twitching, like science nerds who have overdosed on caffeinated drinks). Pyridoxine is the only major water-soluble vitamin with significant toxicity, and even then only at very high doses, where it can cause neurosensory damage.

- **Vitamin B_7 or H (biotin)** is found in a very wide variety of plant- and animal-derived foods and is also produced by your own pet bacteria in the human intestine, so biotin deficiency is virtually unheard of. If you did run low on biotin, it wouldn't be good for your skin and central nervous system though. Biotin is an important cofactor or component of several different carboxylase (CO_2-transferring) enzymes.

- **Vitamin B_9 or M (folic acid or folate)** is most plentiful in leafy green vegetables. (Drat, Popeye wins again...) It is a precursor of tetrahydrofolate (THF), a coenzyme essential for amino acid and nucleotide synthesis. Folic acid deficiency can cause anemia and birth defects, so supplemental folic acid is especially recommended for women who are pregnant or may become pregnant.

- **Vitamin C (ascorbic acid)** is abundant in most fruits. (You're out of luck if you only love bananas though...) It is an essential cofactor for a number of enzymes, including those involved in collagen synthesis, and may play a role as an antioxidant to prevent cellular damage from free oxygen radicals. The classic symptoms of vitamin C deficiency are called **scurvy**, where you talk like a pirate and the inadequate collagen synthesis causes damage to the gums, mucous membranes, and skin.

- **Vitamin B_{12} (cobalamin)** (Fig. 51) is a very close cousin of the porphyrins like heme, except with a cobalt ion instead of an iron ion at the center of the "flower" structure. Despite the close similarity, the human body cannot convert heme to cobalamin or vice versa, and even plants don't know how to make it. Therefore we have to ingest small amounts of cobalamin that was originally made by the intestinal bacteria in other critters and has accumulated in meats, eggs, and dairy products. Like heme, cobalamin is essential for the function of some enzymes, most notably methionine synthase and methylmalonyl CoA mutase. Cobalamin deficiency causes anemia and damage to the central nervous system (numbness, loss of balance, and the tendency for your eyes to glaze over when reading long passages about biochemistry).

Some major water-soluble vitamins (continued)

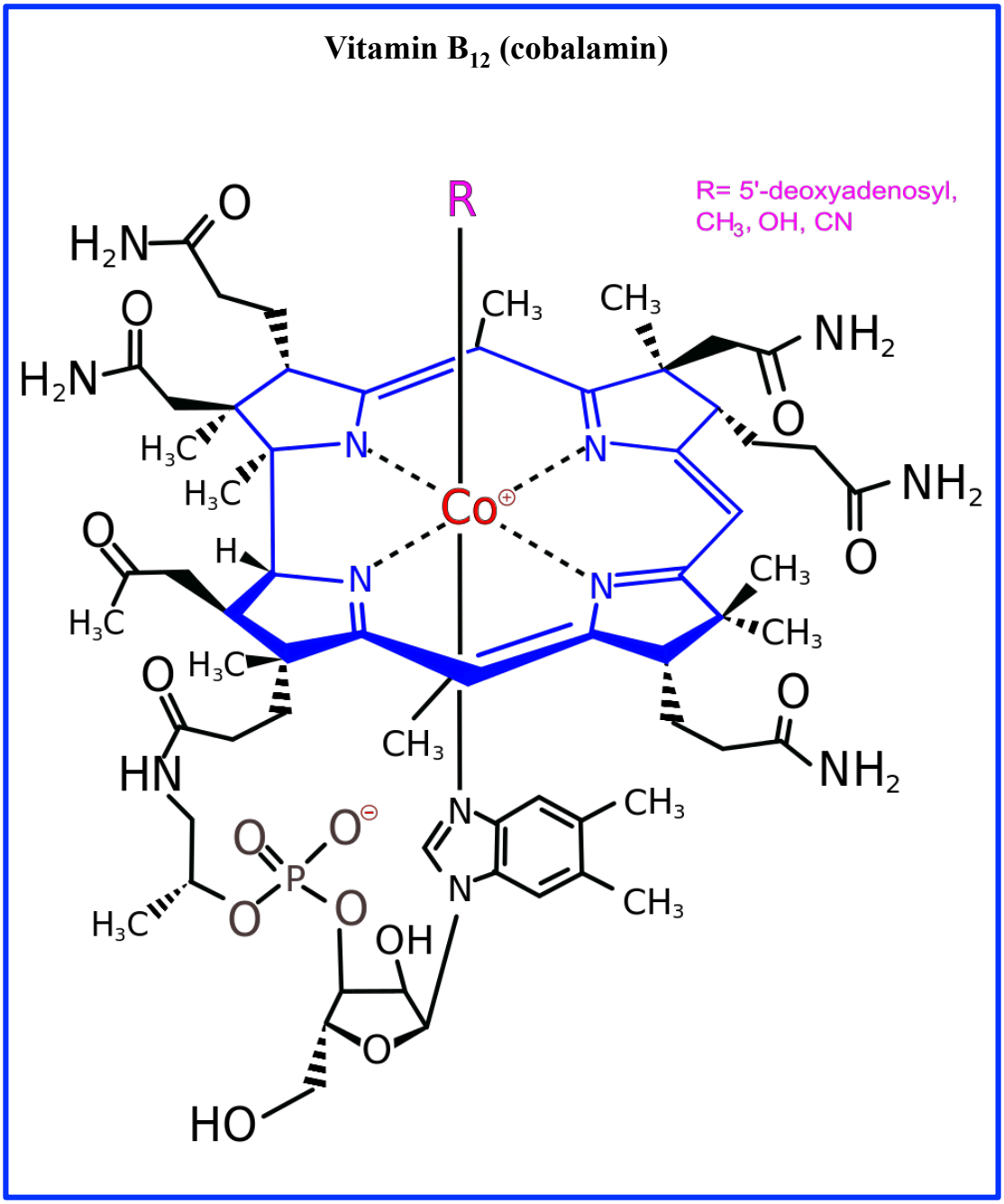


Fig. 51. Water-soluble vitamin B_{12} or cobalamin. (Image from www.wikipedia.org because I'm too lazy to redraw something that scary looking.)

8 Respiration

A common science demonstration is to set sugar on fire; it burns with oxygen (O_2) from the air to produce carbon dioxide (CO_2), water vapor (H_2O), and a large amount of released energy that appears as heat and light. The mitochondria in your cells and other eukaryotic cells (and also many bacteria) use a biochemical process called **respiration** to "burn" sugars and other biomolecules with O_2 to produce CO_2 and H_2O and to release energy. A whole series of enzymes regulate the respiration process very carefully, though, so we we don't heat up and burst into flames but rather convert that released energy into high-energy adenosine triphosphate (ATP) molecules, which can be used to power many other processes inside cells. This section will examine first the mitochondrial structures and then the specific pathways involved in respiration.

8.1 Mitochondria

As shown in Fig. 52, mitochondria are double-membraned organelles that serve as the power plants of eukaryotic cells, consuming carbohydrate fuels and converting that energy into ATP molecules, which are distributed throughout the cell to power everything else in the cell. A cell may contain hundreds or even thousands of mitochondria. Cells that need the most energy, like muscle cells, tend to have the most mitochondria.

Mitochondria appear to have been independent bacteria that invaded ancient cells and developed a symbiotic relationship, with the surrounding host cell providing free room and board for the mitochondria, and the mitochondria providing free energy in the form of ATP for the surround host cell. Over time mitochondria lost many of the genes and features that would allow them to be truly independent organisms, but they retain many signs of their origin.

Fig. 52(b) shows the typical structure of a mitochondrion. Mitochondria are rod-shaped like many bacteria, and have two membranes like Gram-negative bacteria. They have lost any cell wall they may have originally had, presumably to facilitate transport of nutrients and ATP between the mitochondria and the surrounding host cell. Like bacteria, mitochondria have a nucleoid with their own genes, ribosomes to make their own proteins, and storage granules to store some nutrients they keep for themselves. Unlike most bacteria, the inner membrane of mitochondria zigs and zags wildly, which greatly increases its surface area. As will be discussed very shortly, that inner membrane is filled with proteins that convert energy from nutrients into ATP, so maximizing its surface area maximizes the energy that can be converted.

Many bacteria are **aerobic** or oxygen-using and also carry out respiration. The membranes in these bacteria have structures similar to those in mitochondria, so most of this section's discussion of respiration can be applied to aerobic bacteria as well.

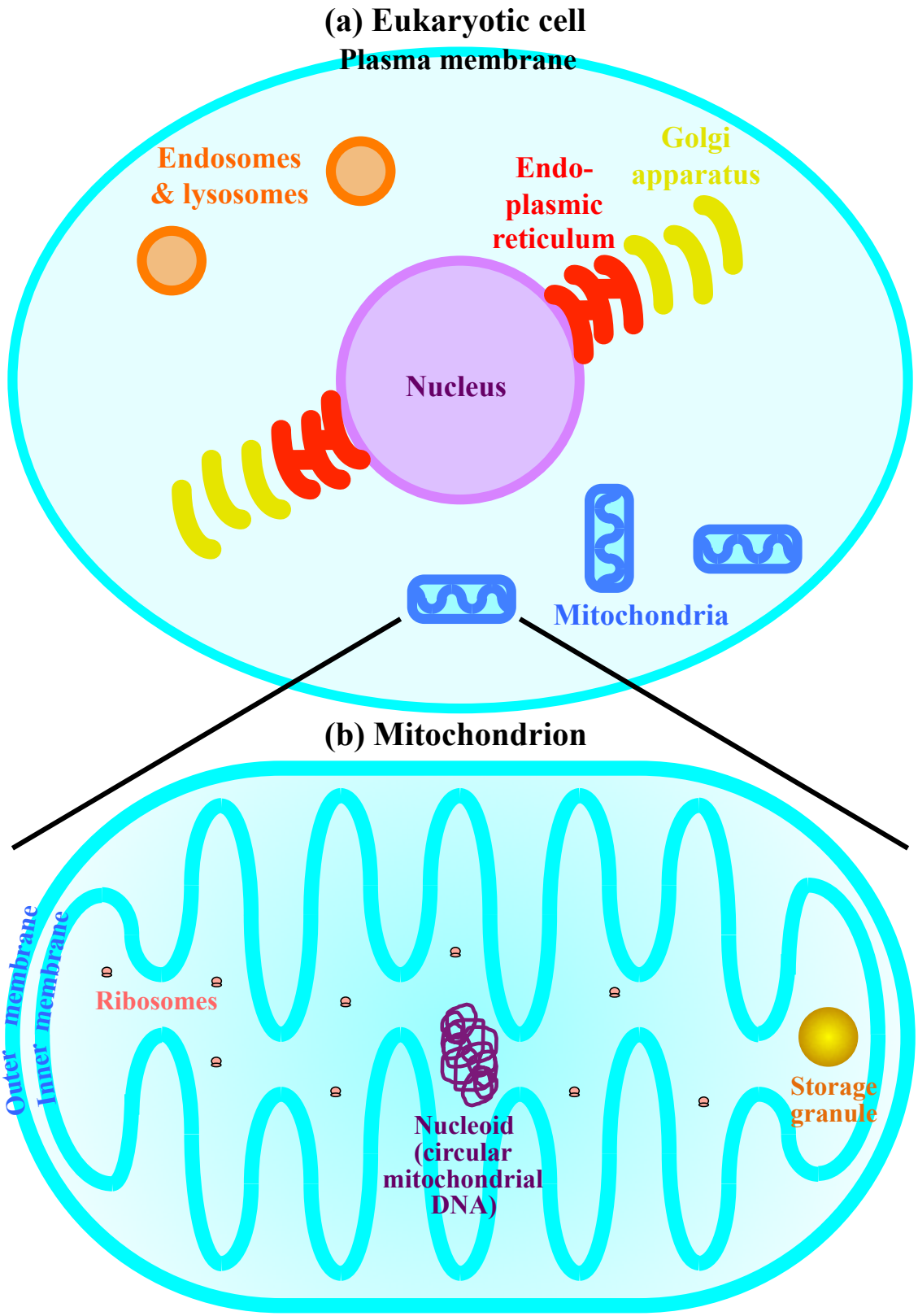


Fig. 52. Structure of (a) a eukaryotic cell and (b) a mitochondrion within that cell.

8.2 Citric Acid Cycle and Oxidative Phosphorylation in Mitochondria

Figure 53 gives an overview of the respiration pathway outside and inside a mitochondrion:

(a) In the cell cytosol outside the mitochondrion, saccharides are converted into glucose ($C_6H_{12}O_6$), which is then split into half-sugars (pyruvate, $C_3H_4O_3$). This process of tearing sugars in half is called **glycolysis** ("sugar splitting") and is shown in Fig. 41:

- The first three enzymes attach negatively charged phosphate (OPO_3^{-2}) groups to each side of the glucose ring.
- The next enzymes use the negatively charged phosphate groups as handles to physically pull the six-carbon glucose ring apart into two three-carbon half-sugars or trioses.
- More enzymes remove the temporary phosphate handles and convert the two three-carbon half-sugars into their final (for this stage) form of two three-carbon pyruvate molecules.
- Along the way, glyolysis produces two energetic ATP molecules and 2 NADH + $2H^+$ (carrying the extra hydrogens [protons + electrons] that were removed from the initial glucose and do not end up in the final pyruvates).

(b) In the central compartment or inner matrix of the mitochondrion, the **citric acid cycle** strips the half-sugars of their hydrogens (protons + electrons) to make carbon dioxide (CO_2), as shown in more detail in Fig. 54. Although the details of the process can look rather scary, here are some of the key points:

- Carbons enter the citric acid cycle as two three-carbon pyruvate molecules, and leave as six single-carbon CO_2 molecules.
- Hydrogens enter the citric acid cycle attached to the two pyruvates ($C_3H_4O_3$) and six water molecules (H_2O) and leave as 8 NADH + $8H^+$.
- Oxygens enter the citric acid cycle attached to the two pyruvates ($C_3H_4O_3$) and six water molecules (H_2O) and leave attached to six CO_2 molecules.
- Along the way, the citric acid cycle produces two energetic ATP molecules.

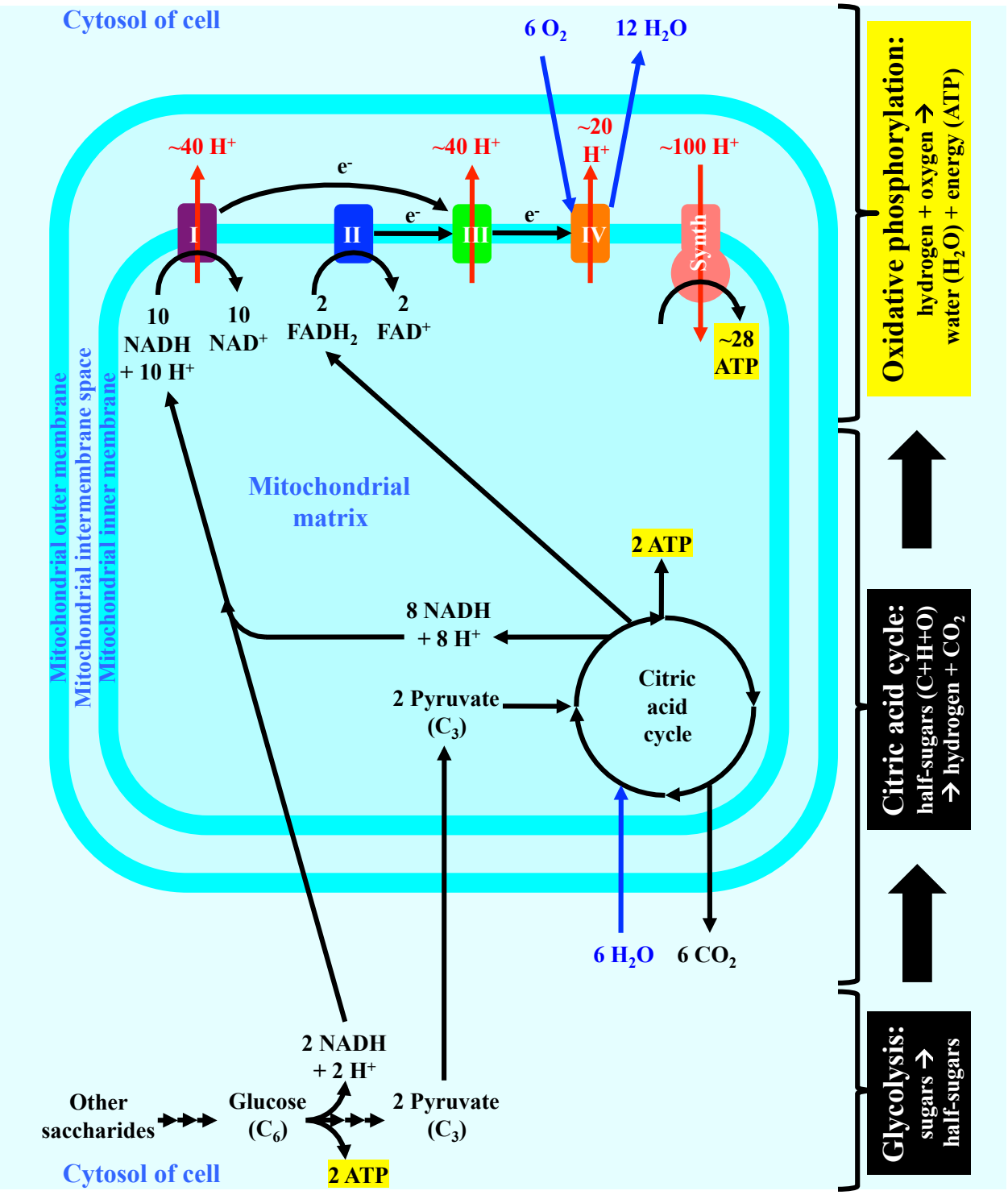


Fig. 53. Respiration pathway in a mitochondrion. In the cell cytosol outside the mitochondrion, saccharides are converted into glucose, which is then split into half-sugars (pyruvate, $C_3H_4O_3$). In the inner matrix of the mitochondrion, half-sugars are stripped of their hydrogen to make CO_2. In the inner membrane of the mitochondrion, that hydrogen is combined with oxygen to produce water (H_2O) plus stored chemical energy (ATP).

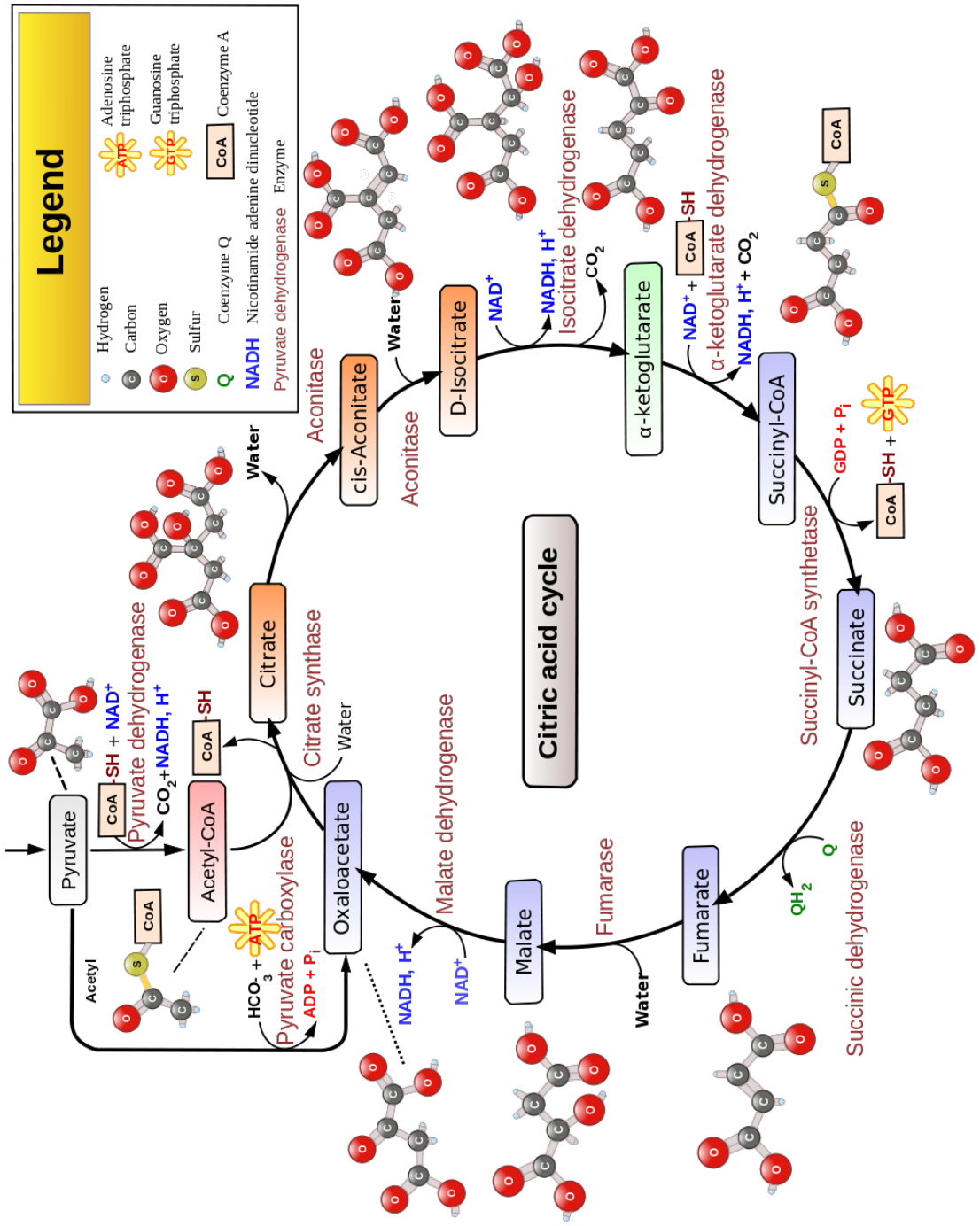


Fig. 54. Respiration pathway in a mitochondrion. In the cell cytosol outside the mitochondrion, saccharides are converted into glucose, which is then split into half-sugars (pyruvate, $C_3H_4O_3$). In the inner matrix of the mitochondrion, half-sugars are stripped of their hydrogen to make CO_2. (Image from https://en.wikipedia.org/wiki/Citric_acid_cycle.)

(c) In the inner membrane of the mitochondrion, that hydrogen is combined with oxygen (O_2) to produce water (H_2O) plus stored chemical energy (ATP). This process is called **oxidative phosphorylation** and is shown in more detail in Fig. 55:

- The electron carrier molecules NADH + H^+ and $FADH_2$ transport energy, electrons, and protons (the components of hydrogen) to cytochrome protein complexes in the mitochondrial inner membrane.

- The electrons and their associated energy are transferred to the first and second complexes in the inner membrane, then passed down from complex to complex to gradually extract energy from the electrons and lower the remaining energy of the electrons (Fig. 55 bottom).

- The inner membrane complexes use energy extracted from the electron to forcibly pump the protons (H^+) from the mitochondrial matrix (the inner mitochondrial compartment) through the inner membrane into the intermembrane space between the inner and outer mitochondrial membranes.

- After the electrons have lost most of their energy, they are added to oxygen (O_2) and protons to form water (H_2O). Twice as much water is produced as was consumed by the citric acid cycle, so there is a net production of water during respiration.

- The herd of protons that were exiled to the intermembrane space are so bunched together that they acidify the intermembrane space to approximately pH 6 and create a net voltage of about 90 millivolts (mV) across the inner membrane. Those protons are sufficiently desperate to get back to the mitochondrial matrix that they are willing to pay to go through a tollgate in the inner membrane. The tollgate is the ATP synthase complex, and it uses the energy toll that it collects from the protons traveling back through it to convert lower-energy adenosine triphosphate (ADP) molecules to higher-energy ATP molecules.

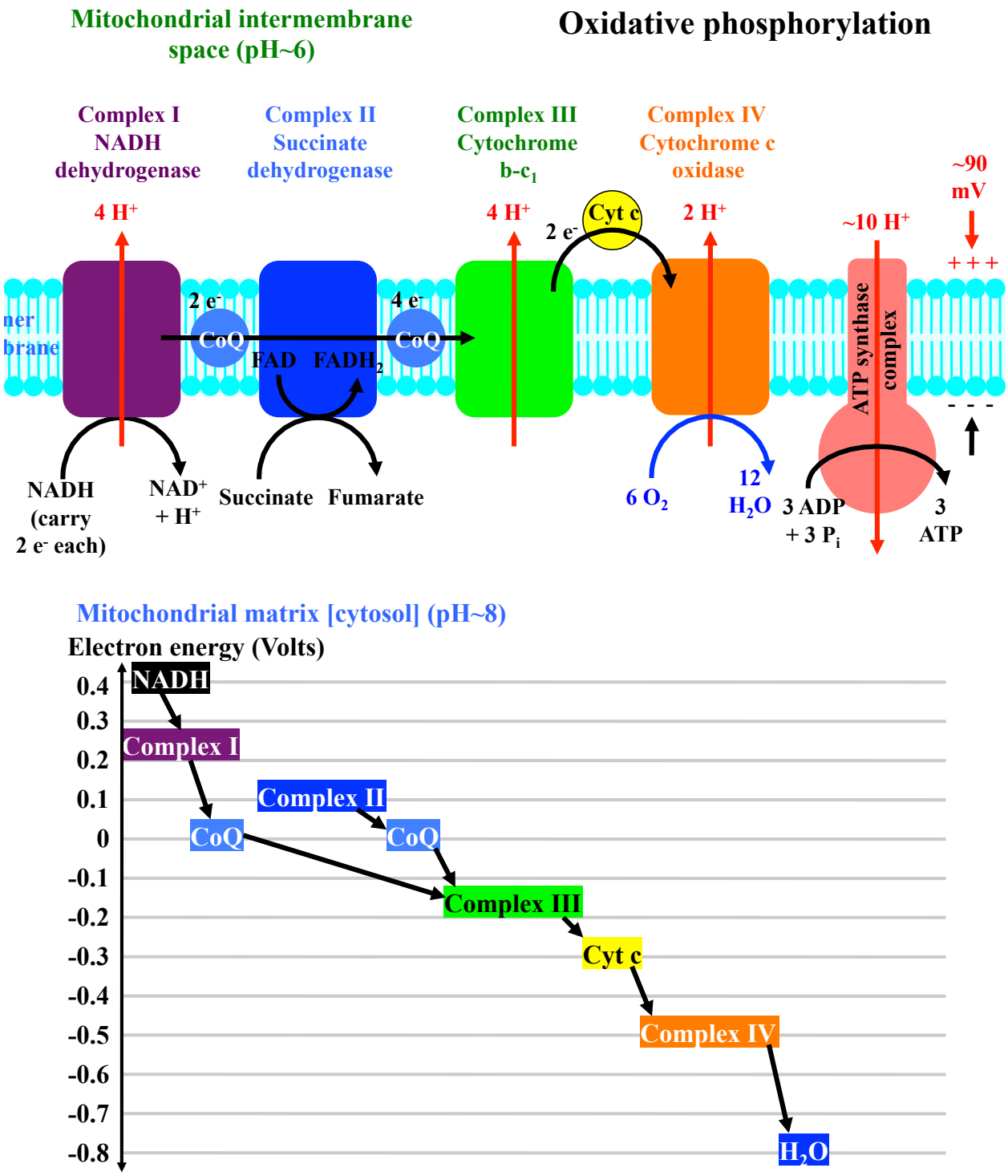


Fig. 55. Respiration pathway in a mitochondrion. In the inner membrane of the mitochondrion, that hydrogen is combined with oxygen to produce water (H_2O) plus stored chemical energy (ATP).

9 Fermentation

Glycolysis, or breaking one glucose molecule into two pyruvate molecules as in Fig. 41, requires no oxygen, produces two ATP molecules of energy, and is done by both **aerobic** cells that use oxygen and **anaerobic** cells that do not use oxygen. As shown in Fig. 53, aerobic cells go on to "burn" those two pyruvate molecules with oxygen to obtain ∼30 more ATP molecules of energy and recharge the NAD^+ molecules used during glycolysis. In the process, the pyruvate molecules get converted all the way into carbon dioxide (CO_2) and water (H_2O). However, anaerobic cells cannot fully break down pyruvate or derive any more energetic ATP molecules from it, so they have to settle for **fermenting** or modifying the pyruvate down just enough to recharge the NAD^+ molecules used during glycolysis. Thus the net yield per initial glucose is ∼32 ATP molecules of energy in aerobic respiration but only 2 ATP in anaerobic fermentation, which is clearly not very energy efficient. There are two different major fermentation pathways that are used in different types of cells (not counting a few weird fermentation pathways in certain specialized bacteria): fermentation to lactic acid, and fermentation to ethanol plus carbon dioxide.

9.1 Fermentation to Lactic Acid

Many anaerobic microorganisms and even a number of animal cells operating under oxygen-deprived conditions can convert the two pyruvate molecules into two lactate or lactic acid molecules without the need for oxygen, as shown in Fig. 56(a). The lactate dehydrogenase enzyme does the magic step of converting the three-carbon pyruvates into three-carbon lactate molecules, recharging the NAD^+ in the process.

Since your mouth is closed most of the time (except for a few people who shall remain nameless), the bacteria in your mouth have plenty of leftover food bits but not much oxygen, so they make lactic acid. That acid can build up to damage your teeth and create cavities, so that led to the evolution of the toothbrush.

Bacteria in milk can also convert the sugar to lactic acid, making the milk acidic (sour) and causing the milk protein (casein) to unfold, clump together, and precipitate out of solution as clumps. That can create anything from buttermilk to yogurt to just plain milk gone bad, depending on the specific bacteria, conditions, and length of time. Bacterial fermentation is also used to acidify everything from pickles to kimchi, thereby preserving them from further bacteria once they become sufficiently acidic.

Vigorous exercise can cause the muscles in an animal or human to use up glucose faster than oxygen can be resupplied from the bloodstream. When not enough oxygen is available, muscle cells switch over from aerobic respiration to anaerobic fermentation to lactic acid. Nonetheless, sprinters can only sprint so far before the lactic acid buildup in their muscles lowers the intracellular pH enough to cause cramps. After the sprinters keel over in pain, the lactic acid slowly leaves the muscle cells, passes through the bloodstream to the liver, gets converted into glucose in the liver and is sent back to the muscles via the bloodstream. Certain other cell types in the body (lens and cornea in the eye, testes, erythrocytes, and many types of cancer cells) can also make use of anaerobic fermentation to lactic acid.

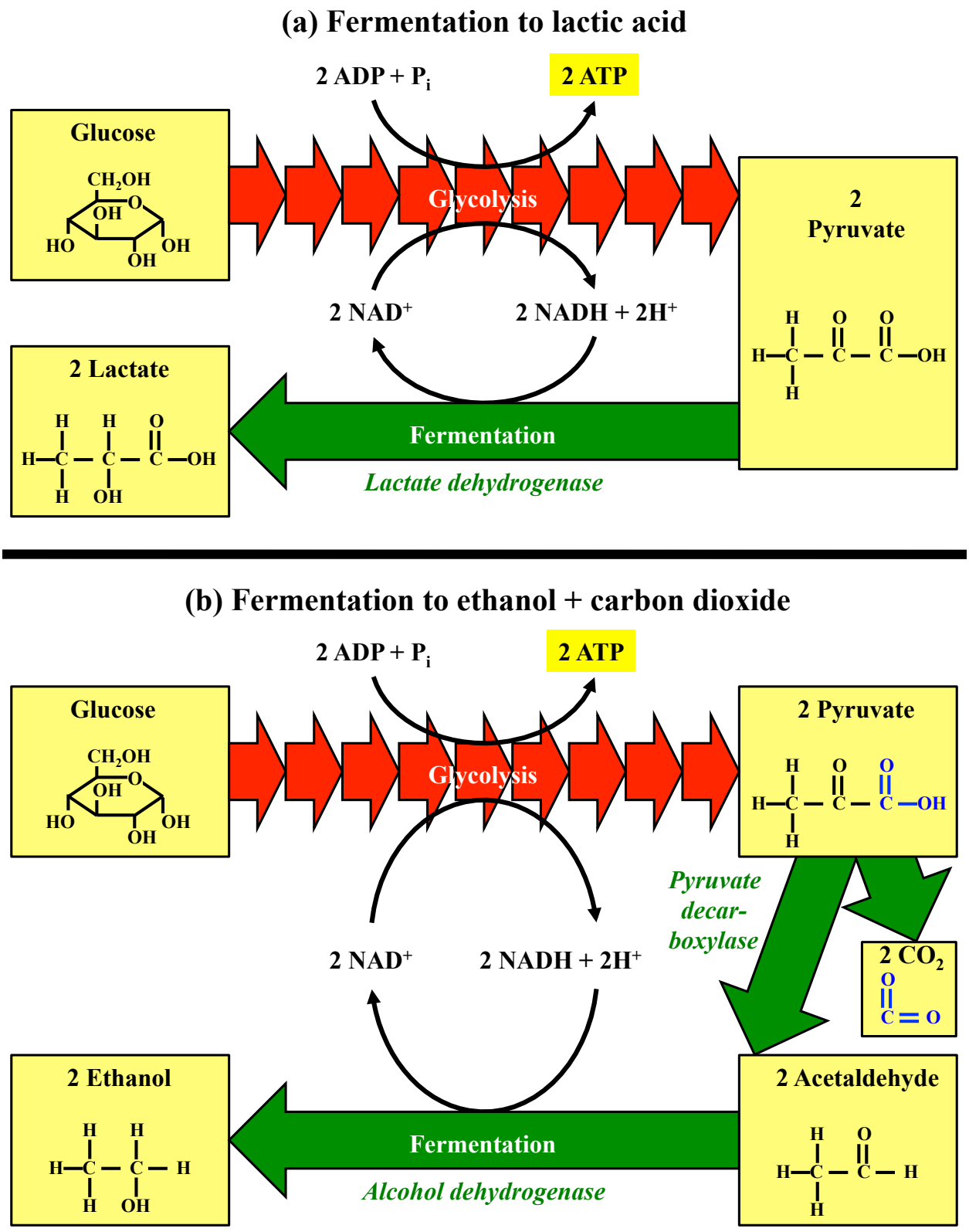


Fig. 56. Fermentation to (a) lactic acid and (b) ethanol plus carbon dioxide.

9.2 Fermentation to Ethanol plus Carbon Dioxide

Other microorganisms, including some bacteria and a wide variety of yeast types, can convert the two pyruvate molecules derived from glycolysis of glucose into two ethanol (ethyl alcohol) molecules plus two carbon dioxide (CO_2) molecules, as shown in Fig. 56(b). The pyruvate decarboxylase enzyme break off the CO_2 molecules, then the alcohol dehydrogenase converts what is left to ethanol and recharges the NAD^+ for more glycolysis. Fermentation to ethanol plus CO_2 is used to convert different types of sugary liquids (juices, etc.) into different alcoholic beverages ranging from beer to wine. The CO_2 production is also used to create gas bubbles that make bread rise (while the resulting alcohol is boiled off during baking). Athough many organisms carry out fermentation to ethanol, the most popular one is *Saccharomyces cerevisiae* (often called *S. cerevisiae*, baker's yeast, or brewer's yeast).

10 Photosynthesis

Photosynthetic reactions in plant chloroplasts convert light energy into stored chemical energy.

10.1 Chloroplasts

Chloroplasts are only present in plant cells, as shown in Fig. 57(a). Like mitochondria (which are also present in plant cells), chloroplasts are double-membraned organelles that are former bacteria now turned into resident power plants inside cells. Whereas mitochondria are power plants that burn carbohydrate fuels to make energy, chloroplasts are solar-powered. They are greener energy, literally.

Figure 57(b) shows a typical chloroplast's structure. The chloroplast is enclosed by outer and inner membranes, but (unlike in mitochondria) the inner membrane is not distended, since nothing terribly important happens on its surface. Instead, most of the magic happens within a third, innermost membrane, in disc-shaped structures called **thylakoids**. Thylakoids contain light-absorbing chlorophyll molecules and do most of the hard work in converting sunlight into stored chemical energy, a process called **photosynthesis**. Thylakoids are arranged into stacks (each stack is called a **granum**) and connected by bridges (called a **lamella**). Like the bacteria from which they descended, chloroplasts have a nucleoid, ribosomes, and storage granules for nutrients (starch).

Chloroplasts appear to be directly related to cyanobacteria, bacteria that produce chlorophyll and use it for photosynthesis, and that are thus often regarded as the simplest form of algae. Presumably some cyanobacteria got stuck inside a larger host cell once upon a time, decided to offer their photosynthetic services in exchange for free room and board in the cell, and then a billion years of botany happened.

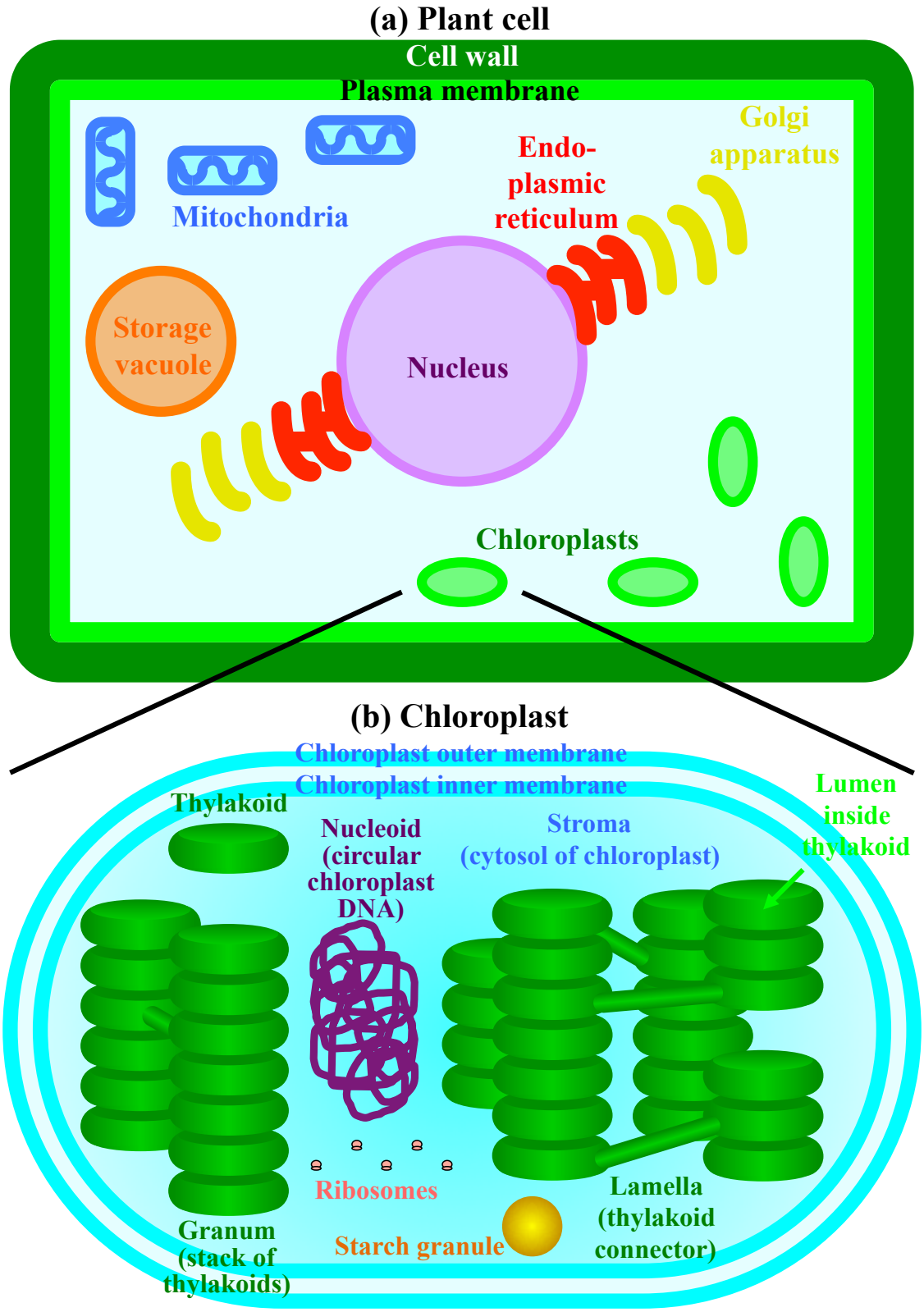


Fig. 57. Structure of (a) a plant cell and (b) a chloroplast within that cell.

10.2 Light and Dark Reactions in Chloroplasts

In the photosynthesis pathway, chloroplasts absorb sunlight and convert that energy into carbohydrate fuels. Those carbohydrate fuels are stored in the cell for later use by the mitochondria, so plants can basically live on light, whereas animals must find external sources of carbohydrates to eat. Figure 58 shows the photosynthetic pathway in a plant chloroplast. Note that the photosynthetic pathway in chloroplasts is basically the respiratory pathway in mitochondria being run in reverse:

(a) In light reactions in the chloroplast's thylakoids, light energy splits water (H_2O) into hydrogen plus oxygen. As the name suggests, these reactions can only happen during daylight. The light reactions are shown in more detail in Fig. 59:

- The electron carrier molecules NADH + H^+ and $FADH_2$ transport energy, electrons, and protons (the components of hydrogen) to cytochrome protein complexes in the mitochondrial inner membrane.

- The electrons and their associated energy are transferred to the first and second complexes in the inner membrane, then passed down from complex to complex to gradually extract energy from the electrons and lower the remaining energy of the electrons (Fig. 59 bottom).

- The inner membrane complexes use energy extracted from the electron to forcibly pump the protons (H^+) from the mitochondrial matrix (the inner mitochondrial compartment) through the inner membrane into the intermembrane space between the inner and outer mitochondrial membranes.

- After the electrons have lost most of their energy, they are added to oxygen (O_2) and protons to form water (H_2O). Twice as much water is produced as was consumed by the citric acid cycle, so there is a net production of water during respiration.

- The herd of protons that were exiled to the intermembrane space are so bunched together that they acidify the intermembrane space to approximately pH 6 and create a net voltage of about 90 millivolts (mV) across the inner membrane. Those protons are sufficiently desperate to get back to the mitochondrial matrix that they are willing to pay to go through a tollgate in the inner membrane. The tollgate is the ATP synthase complex, and it uses the energy toll that it collects from the protons traveling back through it to convert lower-energy adenosine triphosphate (ADP) molecules to higher-energy ATP molecules.

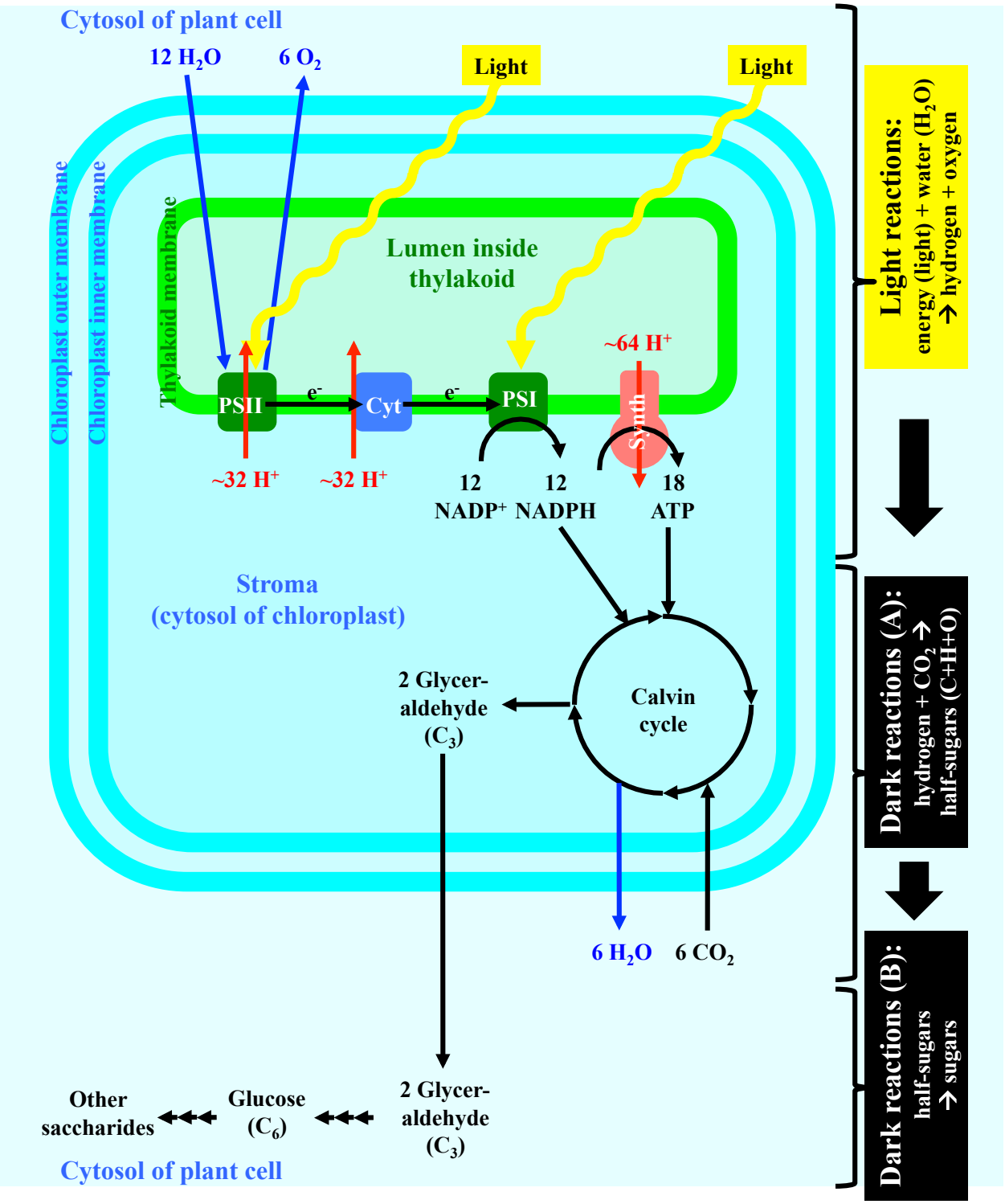


Fig. 58. Photosynthetic pathway in a plant chloroplast. In light reactions in the chloroplast's thylakoids, light energy splits water (H_2O) into hydrogen plus oxygen. In dark reactions outside the thylakoids in the chloroplast, that hydrogen is combined with CO_2 to make half-sugars (glyceraldehyde, $C_3H_6O_3$). In dark reactions in the plant cell cytosol outside the chloroplast, those half-sugars are converted into glucose and other saccharides.

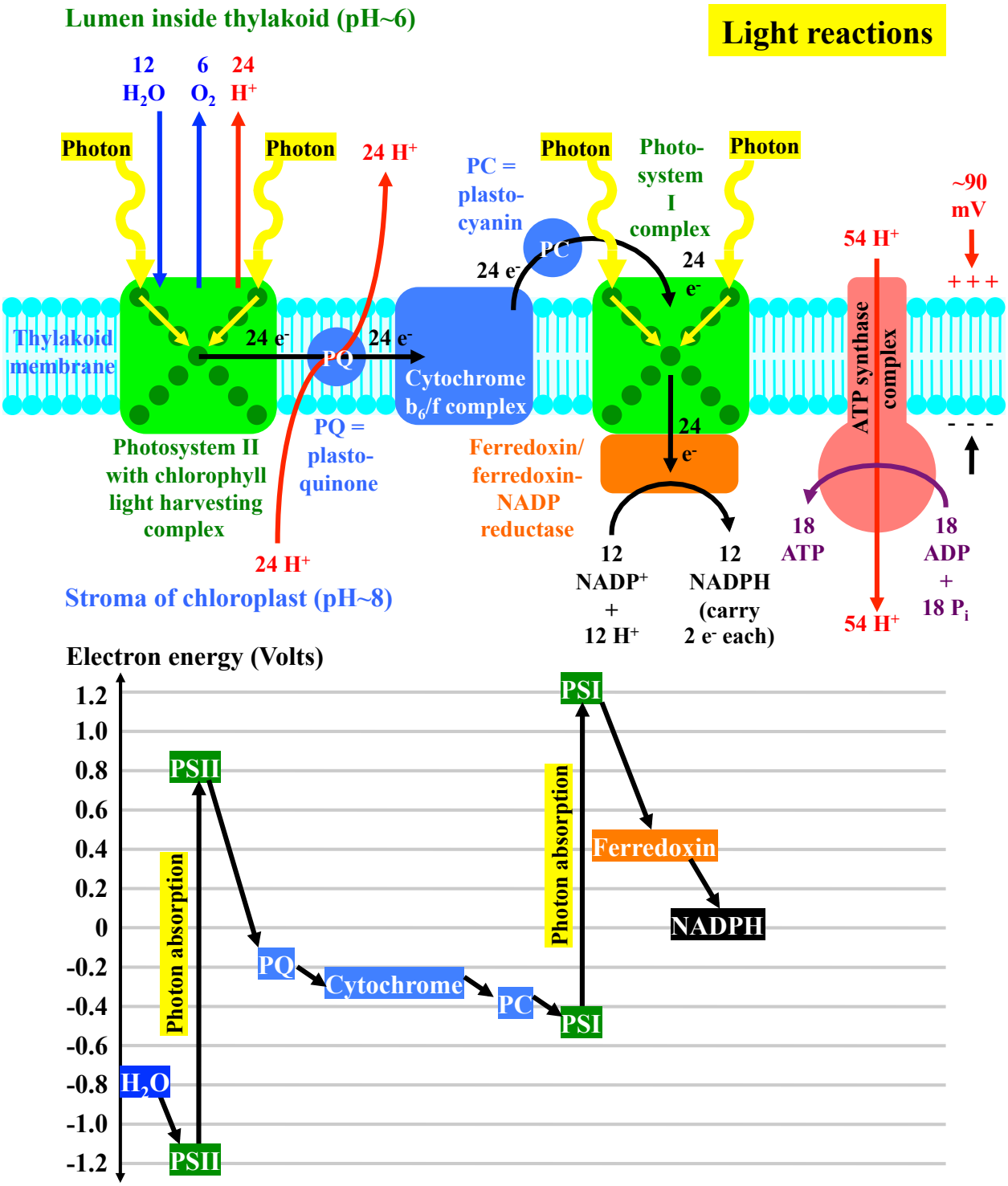


Fig. 59. Light reactions in the photosynthetic pathway. As shown in more detail, in light reactions in the chloroplast's thylakoids, light energy splits water (H_2O) into hydrogen plus oxygen.

(b) In dark reactions outside the thylakoids in the chloroplast, that hydrogen is combined with CO_2 to make half-sugars (glyceraldehyde, $C_3H_6O_3$). As the name suggests, these reactions do not need light and can happen at night (or also during the day). The dark reactions are shown in more detail in Fig. 60:

- Carbons enter the Calvin cycle as six single-carbon CO_2 molecules and leave as two three-carbon glyceraldehyde molecules.
- Hydrogens enter the Calvin cycle as 12 NADPH + $12H^+$ and leave attached to the two glyceraldehydes ($C_3H_4O_3$) and six water molecules (H_2O).
- Oxygens enter the Calvin cycle attached to six CO_2 molecule and leave attached to the two glyceraldehydes ($C_3H_4O_3$) and six water molecules (H_2O).
- Along the way, the Calvin cycle consumes 18 energetic ATP molecules.

(c) In dark reactions in the plant cell cytosol outside the chloroplast, those half-sugars are converted into glucose ($C_6H_{12}O_6$) and other saccharides:

- Enzymes attach a negatively charged phosphate (OPO_3^{-2}) group to each glyceraldehyde half-sugar.
- The next enzymes use the negatively charged phosphate groups as handles to physically squish two glyceraldehyde half-sugars together for form one six-carbon glucose sugar ring.
- More enzymes remove the temporary phosphate handles and ultimately convert glucose into other saccharides.
- Along the way, gluconeogenesis consumes two energetic ATP molecules and 2 NADH + $2H^+$ (carrying the extra hydrogens [protons + electrons] that were not in the initial glyeraldehydes and hat end up in the final glucose).

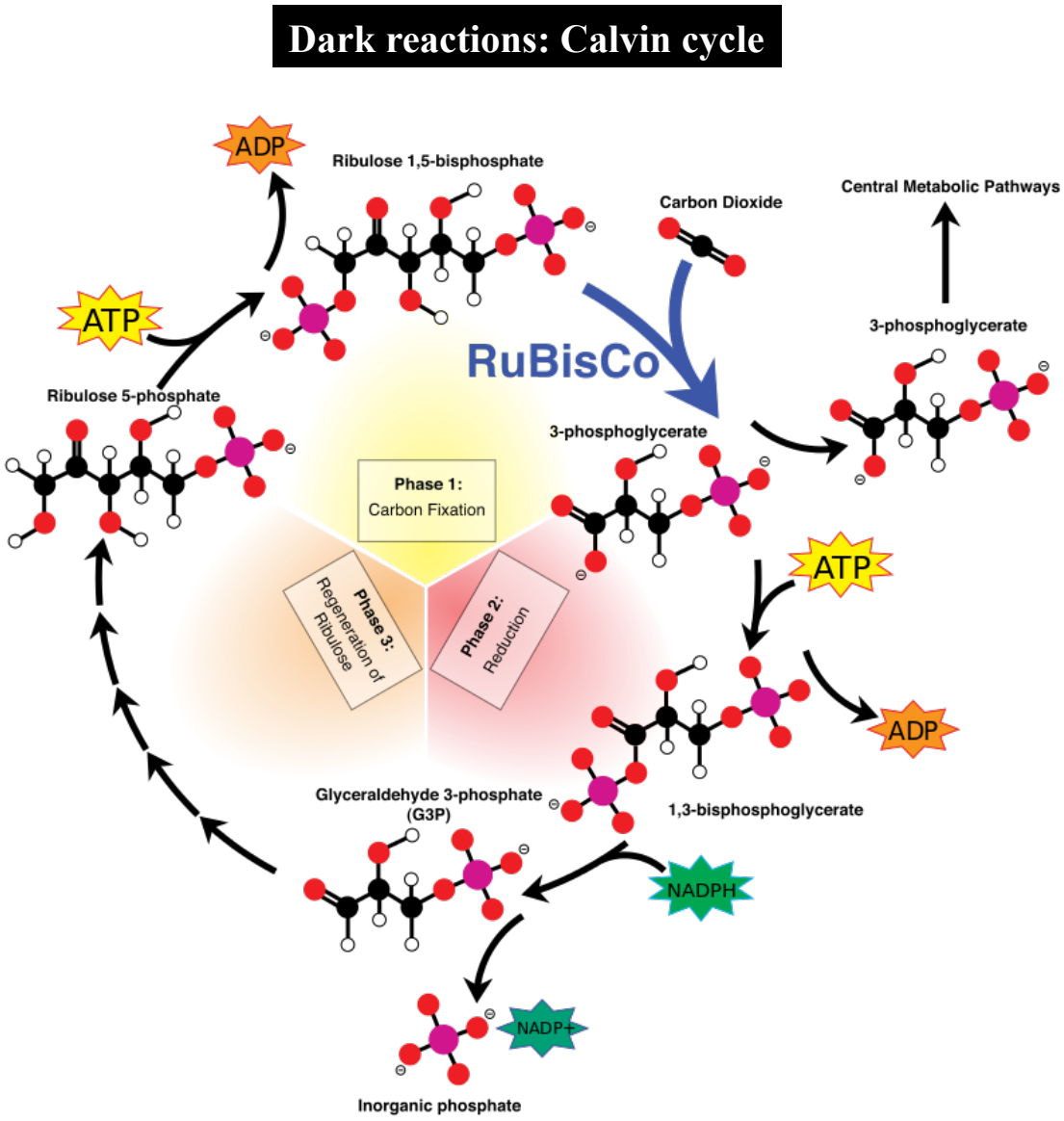


Fig. 60. Dark reactions in the photosynthetic pathway. As shown in more detail, in dark reactions outside the thylakoids in the chloroplast, hydrogen produced in the light reactions is combined with CO_2 to make half-sugars (glyceraldehyde, $C_3H_6O_3$). In dark reactions in the plant cell cytosol outside the chloroplast, those half-sugars are converted into glucose and other saccharides. (Image from https://en.wikipedia.org/wiki/Light-independent_reactions.)

References

[1] Denise R. Ferrier, *Lippincott Illustrated Reviews Biochemistry* (6th ed., LWW, 2013). This is the best introductory textbook on biochemistry, with explanations that are incredibly clear and concise, and illustrations that are amazingly helpful and numerous. This book is aimed at medical school students, so it mentions a number of connections to human diseases, but does not include photosynthesis or much on fermentation.

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[4] Donald Voet, Judith G. Voet, and Charlotte W. Pratt, *Fundamentals of Biochemistry* (4th ed., Wiley, 2012).
These are the three most widely used biochemistry textbooks. They are fairly comparable, but sometimes one gives a better description of some aspect than the other. If you have devoured *Lippincott Illustrated Reviews Biochemistry* and want to learn more details, turn to one of these.

[5] Gerhard Michal and Dietmar Schomburg (eds.), *Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology* (2nd ed., Wiley, 2012). This book is invaluable for graphically showing the "wiring diagrams" of major biochemical pathways.

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