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## Prelude: Biochemistry and the Genomic Revolution

The introductory chapter of *Biochemistry* begins by describing recent advances in this exciting branch of science. We now know the complete genome sequences for several species, and have a nearly complete sequence for human DNA. The implications for biology and medicine are enormous, and they are touched on in this chapter. The authors begin with a brief explanation of the structures of DNA, RNA, and proteins. The unity of biochemistry is an important concept. It means that we can learn about human biochemistry by studying mice, yeast, bacteria, or any living organism. Many biochemical interactions depend on weak noncovalent interactions. Because the great majority of biochemical processes occur in water, the properties of water and their effects on biomolecules are also described. Then follows a discussion of entropy, energy, and the laws of thermodynamics. This provides a basis for understanding hydrophobic interactions and protein folding. Then the authors highlight the impact of biochemistry on modern biology and medicine. Finally, an appendix presents the most popular molecular models and other representations used by biochemists.

## LEARNING OBJECTIVES

When you have mastered this chapter, you should be able to complete the following objectives.

### DNA Illustrates the Relation Between Form and Function (Text Section 1.1)

1. Recognize, name, and draw the four bases used in DNA, and explain the structure of the sugar phosphate backbone.
2. Discriminate between the larger bases, A and G, and the smaller bases, C and T.
3. Describe how the DNA bases pair with each other. Notice that “larger” always pairs with “smaller.”
4. Explain how *base pairing* provides an accurate means for reproducing DNA sequences.
5. Compare the structure of RNA to that of DNA.
6. Define the terms *transcribe* and *translate*.
7. Explain how proteins relate the one-dimensional world of sequence information to the three-dimensional world of biological function.

### Biochemical Unity Underlies Biological Diversity (Text Section 1.2)

8. Describe the evidence for the common origin of all life on Earth.
9. Differentiate between *Archaea*, *Eukarya*, and *Bacteria*.

### Chemical Bonds in Biochemistry (Text Section 1.3)

10. Define the terms *covalent bond*, *resonance structures*, and *arrow pushing*.
11. List the three kinds of *noncovalent bonds* that mediate interactions of biomolecules and describe their characteristics.
12. Describe how the properties of *water* affect the interactions among biomolecules.
13. Explain the origin of *hydrophobic attractions* between *nonpolar molecules* and give examples of their importance in biochemical interactions.
14. State the *first* and *second laws of thermodynamics*. Define the *entropy (S)* and *enthalpy (H)* of a *system*, and give their mathematical relationship.
15. Explain how protein folding is affected by changes in entropy and free energy.

### Biochemistry and Human Biology (Text Section 1.4)

16. Discuss the most important achievements of *biochemistry* in the elucidation of the *molecular basis of life* and in the advancement of modern biology and medicine.

## Appendix: Depicting Molecular Structures

17. Explain the uses of different *molecular models*.
18. Relate the planar *Fischer projection* to the tetrahedrally arrayed substituents around a carbon atom.

## SELF-TEST

### DNA Illustrates the Relation Between Form and Function

1. Which base is *not* found in DNA's building blocks?
  - (a) uracil
  - (b) thymine
  - (c) cytosine
  - (d) guanine
  - (e) adenine
2. The DNA sequence AAA would pair with the sequence
  - (a) AAA.
  - (b) GGG.
  - (c) CCC.
  - (d) TTT.
3. RNA differs from DNA because RNA (select all correct answers)
  - (a) is usually single stranded.
  - (b) often base-pairs with itself (intrastrand pairing).
  - (c) uses deoxyribose instead of ribose.
  - (d) uses uracil instead of thymine.
  - (e) forms a triple helix instead of a double helix.
4. In the genetic code, a sequence of how many bases codes for one amino acid?
  - (a) 2
  - (b) 3
  - (c) 5
  - (d) 7

### Biochemical Unity Underlies Biological Diversity

5. Which of the following molecular patterns or processes are common to both bacteria and humans?
  - (a) development of tissues
  - (b) information flow from proteins to DNA
  - (c) the "energy currency"
  - (d) genetic information flow
  - (e) similar biomolecular composition
6. The distinguishing feature of the Eukarya is that
  - (a) they are all multicellular.
  - (b) they have tough cell walls around each cell.
  - (c) they have a well-defined nucleus within each cell.
  - (d) they are more primitive than the Archaea or the Bacteria.

## Chemical Bonds in Biochemistry

7. For the bonds or interactions in the left column, indicate all the characteristics in the right column that are appropriate.
- |                               |  |
|-------------------------------|--|
| (a) electrostatic interaction | (1) requires nonpolar species                        |
| (b) hydrogen bond             | (2) involves charged species only                    |
| (c) van der Waals bond        | (3) requires polar or charged species                |
| (d) hydrophobic interaction   | (4) involves either O and H or N and H atoms         |
|                               | (5) involves polarizable atoms                       |
|                               | (6) is also called a <i>salt bridge</i>              |
|                               | (7) exists only in water                             |
|                               | (8) is optimal at the van der Waals contact distance |
|                               | (9) has an energy between 3 and 7 kcal/mol           |
|                               | (10) has an energy of around 1 kcal/mol              |
|                               | (11) is weakened in water                            |
8. The properties of water include
- the ability to form hydrophobic bonds with itself.
  - a disordered structure in the liquid state.
  - a low dielectric constant.
  - being a strong dipole, with the negative end at the O atom.
  - a diameter of 5 Å.
9. Biological membranes are made up of phospholipids, detergent-like molecules with long nonpolar chains attached to a polar head group. When isolated phospholipids are placed in water, they associate spontaneously to form membrane-like structures. Explain this phenomenon.
10. If two molecules had a tendency to associate with each other because groups on their surfaces could form hydrogen bonds, what would be the effect of putting these molecules in water? Explain.
11. Which of the following statements is correct? The entropy of a reaction refers to
- the heat given off by the reaction.
  - the tendency of the system to move toward maximal randomness.
  - the energy of the transition state.
  - the effect of temperature on the rate of the reaction.
12. What are the three main noncovalent interactions that contribute to the folding of proteins into specific shapes?

## Biochemistry and Human Biology

13. According to the chapter, which diseases are understood at a molecular level because of advances in biochemistry and molecular biology?
- sickle-cell anemia
  - cystic fibrosis
  - hemophilia
  - alcoholism
  - schizophrenia

**Appendix: Depicting Molecular Structures**

14. Match the types of molecular models in the left column with the appropriate application in the right column.
- |                          |   |
|--------------------------|---|
| (a) space-filling model  | (1) shows the bond framework in macro molecules         |
| (b) ball-and-stick model | (2) indicates the volume occupied by a bio-molecule     |
| (c) skeletal model       | (3) shows the bonding arrangement in small biomolecules |
15. Hydrogen atoms are frequently omitted from ball-and-stick models and skeletal models of biomolecules. Explain why.

**ANSWERS TO SELF-TEST**

- a
- d
- a, b, d
- b
- c, d, e
- c
- (a) 2, 6, 9, 11 (b) 3, 4, 9, 11 (c) 5, 8, 10 (d) 1, 7. Hydrophobic interactions are strengthened in water.
- d
- When the nonpolar chains of the individual phospholipid molecules are exposed to water, they form a cavity in the water network and order the water molecules around themselves. The ordering of the water molecules requires energy. By associating with one another through hydrophobic interactions, the nonpolar chains of phospholipids release the ordered water by decreasing the total surface area and hence reduce the energy required to order the water. Such coalescence stabilizes the entire system, and membrane-like structures form.
- Because of the high dielectric constant of water and its ability to form competing hydrogen bonds, the interaction between the molecules would be weakened.
- b
- The book mentions the hydrophobic effect, hydrogen bonds, and van der Waals interactions as contributing to protein folding.
- a, b, c. After many decades of work, the puzzle of human alcoholism and schizophrenia have evaded easy biochemical explanation. There is good evidence of genes that produce increased alcohol consumption in experimental animals. In humans, free will gets in the way of clear experimental results. The genetics of alcohol preference in mice is discussed in an article from Lee M. Silver's lab in *Mamm. Genome* 9, 942 (1998) by J. L. Peirce et al., and in Chapter 18 of the excellent book *Time, Love, Memory*, by Jonathan Weiner.
- (a) 2, (b) 3, (c) 1

15. The ball-and-stick model and skeletal model best show the bonding arrangements and the backbone configurations of biomolecules; the inclusion of the numerous hydrogen atoms would obscure the very features revealed by these models.

## PROBLEMS

1. Proteins have 20 building blocks (amino acids) and DNA has only four (nucleotides), yet the “messages” in the two sequences have the same information content and are translatable. Could there be an informational molecule with even fewer than four building blocks?
2. The three roles of RNA described in the text all deal with protein synthesis, that is, making chains of amino acids having the correct sequence. Describe the three jobs of RNA in this process.
3. As will be seen in succeeding chapters, enzymes provide a specific binding site for substrates where one or more chemical steps can be carried out. Often these sites are designed to exclude water. Suppose that at a binding site, a negatively charged substrate interacts with a positively charged atom of an enzyme.
  - (a) Using Coulomb’s equation, show how the presence of water might affect the interaction. What sort of environment might be preferable for an ionic interaction? Note that a numerical answer is not required here.
  - (b) How would an ionic interaction be affected by the distance between the oppositely charged atoms?
4. In some proteins the contact distance between an amide hydrogen and a carbonyl oxygen that are participating in hydrogen binding is somewhat less than expected from adding their respective van der Waals contact distances. What feature of hydrogen bonding allows the two atoms to be closer to each other?
5. Water molecules have an unparalleled ability to form hydrogen bonds with one another. Water also has an unusually high heat capacity, as measured by the amount of energy required to increase the temperature of a gram of water by 1° C. How does hydrogen bonding contribute to water’s high heat capacity?
6. The oxygen-carrying protein myoglobin is composed of 153 amino acids, linked by covalent bonds into an unbranched polymeric chain. If all amino acids in the chain assume a regular and periodic conformation in which each residue is separated from the next by a distance of 1.5 Å, then the molecule could be as long as 230 Å (153 residues × 1.5 Å per residue). Analysis of the myoglobin molecule in solution reveals that it is no more than 45 Å in length. What does this observation tell you about how a linear polymer of amino acids might behave in solution?
7. The Second Law of Thermodynamics states that the entropy (disorder) of a system and its surroundings always increases for a spontaneous process. So why do proteins fold up spontaneously? It is evident that protein folding moves from a disorderly state (randomly unfolded proteins) to an orderly state (folded proteins). Explain.

8. The text states that genetically engineered bacteria can be used as “factories” to produce insulin and other valuable proteins. Where did insulin come from for the treatment of diabetes before genetic engineering was developed?

## ANSWERS TO PROBLEMS

1. A good analogy is the alphabet (26 letters) versus Morse Code (three symbols—dot, dash, and space). Any thought that can be expressed in English can be written out using the 26 letters, or can be translated into Morse Code. The Morse Code requires a longer string of symbols to express the same message as the alphabet, but it works. So we could imagine as few as two symbols—when letters are encoded in a computer, the storage is binary, with each bit being “off” or “on.”
2. RNA provides the “factory” for protein synthesis—the ribosome is about half RNA, and owes its functionality to ribosomal RNA. It provides the “message” or “blueprint” for every protein synthesized, in the form of mRNA or messenger RNA. And it “translates” the mRNA message into amino acids using “adaptor” molecules of transfer RNA, which bring the amino acids one by one into the ribosome “factory.”
3. (a) The magnitude of the electrostatic attraction would be diminished by the presence of water because  $D$ , the dielectric constant, is relatively high for water. Inspection of Coulomb’s equation shows that higher values of  $D$  will reduce the force of the attraction. Lower values, such as those for hydrophobic molecules like hexane, allow a higher value for  $F$ . We shall see that many enzyme active sites are lined with hydrophobic residues, creating an environment that enhances ionic interaction.  
(b) Inspection of Coulomb’s equation also reveals that the force between two oppositely charged atoms will vary inversely with the square of the distance between them.
4. Both atoms have partial charges that attract each other. The single electron of the hydrogen atom is partially shifted to the nitrogen atom to which the hydrogen is covalently bound. As a result, the distance between the electronic shells of the hydrogen and the carbonyl oxygen is reduced, allowing them to approach each other more closely.
5. When water is heated, considerable energy is required to break the hydrogen bonds. Only after a large percentage of bonds are broken are the molecules more mobile and the temperature raised. This buffering capacity of water is very important to cells, which can resist changes caused by increases in temperature because of water’s high heat capacity.
6. Because the length of the myoglobin molecule in solution is much less than its extended length, it is likely that the polymeric chain is folded into a compact structure. This conclusion was first reached in the 1930s when studies on the radius of gyration of certain proteins showed that they are shorter than their predicted length. The globular structure of a soluble protein was visualized in detail by John Kendrew in 1957 when he used x-ray analysis to show that myoglobin is an assembly of rodlike chains with overall dimensions of  $45 \times 35 \times 25 \text{ \AA}$ . It is now well established that

most soluble proteins fold into globular, compact structures in solution. Discussion of those folded structures as well as how they undergo folding will be discussed at length in the text. (Kendrew, J. C. et al., *Nature* **181**:662 [1958].)

7. As explained in the chapter—folded globular proteins have a hydrophobic interior. The process of folding releases water molecules, which would have been otherwise kept hydrogen bonded to the protein chain. Thus the “surroundings” have an increased entropy although the “system”—the protein itself—has a decrease. The negative (favorable) enthalpy changes when weak bonds form as a protein folds correctly also tend to result in a favorable (negative) free-energy change.
8. Insulin had to be purified from cow, sheep, pig, etc. The pancreatic glands were collected from slaughter-houses. It was not unusual for people to develop allergies to these foreign types of insulin. Modern methods allow production of the human form of insulin in large quantities and high purity, a very clear improvement over the old system.