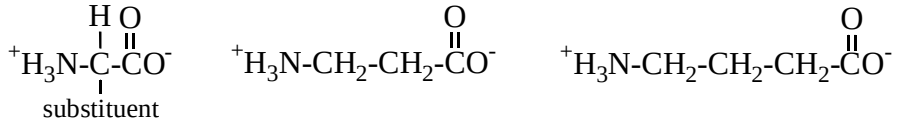
Chapter 20 – Proteins

The previous two chapters, Carbohydrates and Lipids, have dealt with substances with a primary mission to provide energy to the body. Lipids are also the primary constituents of cell membranes. In contrast, although we can obtain energy from proteins, this is not a major function they serve. As a molecular class, proteins and polypeptides (the primary difference is molecular length) are jack-of-all-trades molecules. Each protein/polypeptide/peptide will have only one, very specific function, but those functions range from fighting infections to carrying oxygen through the blood to being the major constituent of hair. We will begin by considering their chemical composition, then proceed to an examination of their structure. Along the way and at the end we will look at various proteins and the bodily functions they serve. As a final note, relatively few structures in this chapter are dealt with using their chemical structures. For that reason, you will need to have your book available as you read these notes. I don't have the capability of drawing many of the structures you will see in this chapter.

20.1 Amino Acids. The Building Blocks of Proteins

Proteins, polypeptides, and peptides are all composed of a string of α-amino acids. As the name suggests amino acids are compounds that contain an amine group ($-NH_2$) and an acid group ($-CO_2H$). The "α" refers to the relative locations of these groups. In α-amino acids, the $-NH_2$ and $-CO_2H$ groups are attached to the same carbon. In β-amino acids these groups are on adjacent carbon atoms and in γ-amino acids there is a carbon between the carbons to which they are attached. An interesting and important structural feature of amino acids is that the acid group on the molecule transfers its proton to the base group. Thus, although the molecule remains electrically neutral, it has two charged groups within it. The following pictures show α-, β-, and

γ-amino acids.



α-amino acids β-amino acids γ-amino acids

Only α-amino acids appear in proteins, polypeptides, and peptides so we will only discuss those in the future. (Substituents can replace a carbon-bound hydrogen in β- and γ-amino acids.) For that reason, unless otherwise stated, assume that the term "amino acid" refers to "α-amino acid."

The amino acids that comprise proteins and peptides come from the consumption (eating) of proteins and peptides and from production within our bodies. Those amino acids that our bodies cannot produce are called essential amino acids, while those that it can are called non-essential. In the typical diet meats provide these materials, although certain plants (particularly beans) provide can substitute for meat. When we eat meat, our body breaks the protein down into its constituent amino acids, then reassembles them into ones our body uses. Since we are animals too, the ratio of different amino acids in our diets is similar to those we need. The result is that a diet that includes meat provides us with our amino acid needs without effort.

If one chooses a vegetarian diet, one must be careful in selecting protein sources. The amino acids appearing in plant proteins typically occur in different ratios from our bodily needs. Complicating a vegetarian diet is the fact that our body cannot store amino acids. Excess amino acids are either burned for fuel or excreted. This means that vegetarians must blend protein sources from different plants on a regular basis. (This is not as big an inconvenience as one might imagine. Just like you don't need to eat meat at each meal, one doesn't need to get the protein balance just right at each meal.) Furthermore, dairy products can provide an animal

based protein source. Around the world, most people live on diets that are completely vegetarian or very nearly so for economic reasons. In these cultures, specific food combinations generate the right balance of amino acids. Two such combinations are tofu/rice and tortilla/refried beans.

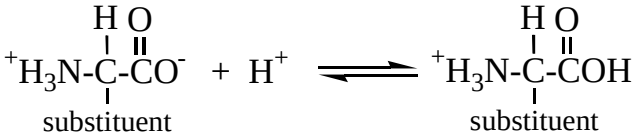
When your body digests protein, all the amino acids it uses to recreate peptides and proteins fall into a group of 20 amino acids called the standard amino acids. A table listing them is provided on p. 569 of your textbook. Other amino acids appear in proteins and peptides in your body, but all of these are derived from a standard amino acid. That is, once a standard amino acid is incorporated into a peptide or protein it is altered to a different amino acid. We'll return to this later in the notes.

We now need to discuss some properties of amino acids. As you know, amines are weak bases and carboxylic acids are weak acids. When amino acids form, the carboxylic acid proton is transferred to the amine group. A molecule containing both a positively and negatively charged group is called a zwitterion. The pH of this solution depends on how strong the acid and base are relative to one another. If the acid was stronger the pH will be less than 7, while if the base were stronger the pH would climb to above 7. Can you figure out how changing the substituent would cause the relative strengths of the acid and base to change?

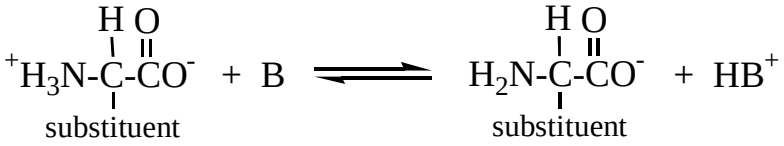
That amino acids exist as zwitterions affects their properties. For example, if glycine existed as $H_2NCH_2CO_2H$ do you think it would be a solid, liquid, or gas? It would probably be a liquid. Propionic acid, $CH_3CH_2CO_2H$, is a liquid and weighs just a little more. Butyl amine, $CH_3CH_2CH_2NH_2$, weighs a bit less, and is also liquid. Thus, the fact that all standard α-amino acids are solids is a function of their existence as zwitterions.

If two electrodes are placed in a solution of sodium chloride and one is charged positively (anode, see p. 204 of your textbook) and the other negatively (cathode), the sodium ions will be

drawn to the cathode and the chloride ions to the anode. This is true of any ionic species. What about the zwitterionic amino acids? Since each molecule of an amino acid is electrically neutral (the positive and negative charges offset) none will be drawn preferentially towards either electrode. This pH is called the isoelectric point (pI). If we lower the pH below pI, then there are excess protons available to add to the weak base $-CO_2^-$:



The product molecule is no longer electrically neutral and would be drawn towards the cathode. In very highly acidic solutions, only the ion on the right would exist, but typical biological solutions (e.g. blood) never become very acidic (or basic, *vide infra*). So that as solutions become more acidic than pI, an equilibrium exists between the two species.
If the pH of a solution is raised above the pI, a proton is removed from the weak acid $-NH_3^+$.



Again, the product carries an electrical charge and, in this case, is pulled to the anode. In biological fluids, the pH will never be so basic as to drive the reaction all the way to the right, so the reaction will exist as an equilibrium in most situations.

At the pI almost every molecule is electrically neutral (no excess or deficiency of H^+). This is because at the pI, both of the equilibria just described operate. Thus while the large majority of amino acid molecules exist as the zwitterion, small, but equal, amounts exist as the protonated and deprotonated forms. We'll return to this topic in Section 20.3.

There are a number of ways to classify the side chains (substituents). One way is to group them according to their interaction with water (i.e. solubility). Nonpolar side chains include all

of those in the first group in Table 20.1 (p. 569, textbook) and methionine from the sulfur side-chains group at the bottom of the table. These hydrophobic side chains interact poorly with water. Almost half (9) of the amino acids contain nonpolar side chains. A second group includes polar side chains. Some are "neutral" (i.e. not acidic or basic). These molecules include all of the side chains with alcohols and amides. Cysteine is frequently included with this group, although sometimes it is placed in the nonpolar group. Others incorporate acidic and basic side chains. These amino acids include an extra carboxylic acid or amine group, respectively.

Summarizing

nonpolar – alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, proline, methionine

polar neutral – glycine, serine, threonine, tyrosine, asparagine, glutamine, cysteine

polar acidic – aspartic acid, glutamic acid

polar basic – lysine, arginine, histidine

Cysteine has the special property of being able to form a disulfide linkage. In Chapter 13, Section 6 (p. 12 notes, p. 420 textbook) we learned that thiols readily oxidize to disulfides. When amino acids with nonpolar side chains are dissolved in water, they tend to associate with the nonpolar side chains grouping together (somewhat like a micelle (p. 9 Chapter 19 notes)). These interactions are usually weak and, therefore, fluid. A disulfide linkage is a covalent bond and, hence, much stronger. Thus disulfide linkages have a prominent role in maintaining the three-dimensional structure of proteins.

Finally, all but one standard amino acid is optically active. Look at table 20.1 and try to figure out which one isn't. The requirement for a molecule to be optically active is for it to have a chiral center and that (usually) requires four different groups bound to a tetrahedral carbon.

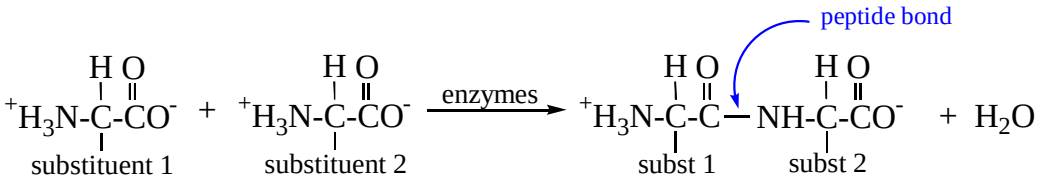
Glycine has two hydrogens bound to the α carbon and that is the only tetrahedral center in the molecule, so glycine is achiral. Almost all naturally occurring amino acids are L-amino acids.

20.2 Overview of Protein Structure

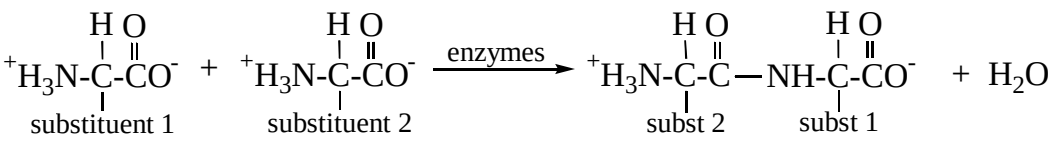
All proteins have 3 levels of structure, some have 4. As we shall see, peptides will generally have only one or two levels of structure. Level 1 structure is simply the sequence of attached amino acids in the chain (remember proteins are amino acid polymers). Level 2 structure (short-range) results from the interactions between small groups of amino acids along the chain. Level 3 structure (long-range) results from the interactions between level 2 structures. Level 4 structure results from 2 separate protein chains interacting. Thus, for proteins that function in the absence of other proteins, this level of structure is missing.

20.3 Primary Structures of Proteins

To generate a polymer, we must first see how the amino acids combine to form a larger structure. Reaction of the amine end of one amino acid, with the acid end of a second amino acid yields a special type of amide bond, called a peptide bond. A molecule containing only two amino acids linked by an amide bond is called a dipeptide.



A natural question that follows from this picture is "Can the peptide form in the other direction?" i.e.:



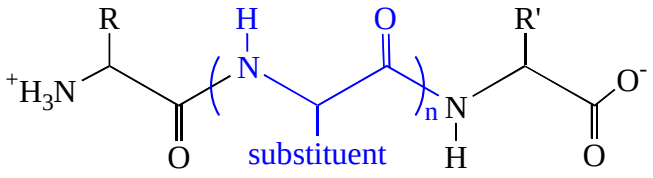
As you might have expected, the answer is yes (although a different set of enzymes must catalyze the reaction). After amino acids have combined to form part of a peptide they are referred to as amino acid residues.

We now need to go over a few definitions. Peptides, polypeptides, and proteins differ in that they contain different numbers of amino acids in their primary structure chain. A peptide is composed of 2 – 10 amino acids, while a polypeptide ranges from 10 – 50. Fifty or more amino acids make up proteins. Please remember these are not hard-and-fast numbers (except the lower limit of 2 for peptides). Different individuals use different ranges.

Enzymes construct peptides, polypeptides, and proteins. Consider glycine and alanine. An enzyme that begins a peptide glycine-alanine is incapable of generating the reverse combination at the beginning. It is this property that allows the body to construct very specific amino acid sequences from the standard amino acids. This specificity is required because the 20 standard amino acids can generate almost 400 different dipeptides (~20^2) and almost 8000 tripeptides (~20^3). The number of possible combinations for a protein is mind-boggling.

A single enzyme cannot generate an entire protein, but it will produce peptides that other enzymes will combine into polypeptides, and still others will construct the protein. To simplify writing out peptide/protein amino acid sequences, 3-letter abbreviations are used for each amino acid. Thus glycylalanine shortens to gly-ala.

Like all polymers peptides and proteins have a “backbone” that runs the length of the molecule. The polymers discussed in Chapter 12 (p. 10 notes) all had a carbon backbone with all C-C single bonds. Proteins have a more elaborate backbone because of the presence of peptide (amide) bonds. Their backbone looks like:

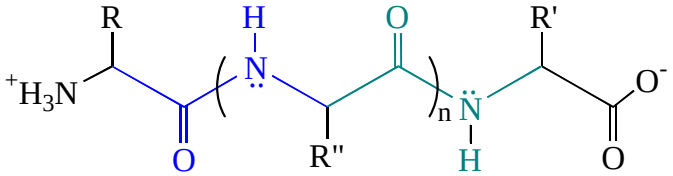


Adding an amino acid to the end of the existing peptide expands the peptide. By convention, for amino acids through proteins, the amine part is written to the left and the carboxylate group to the right.

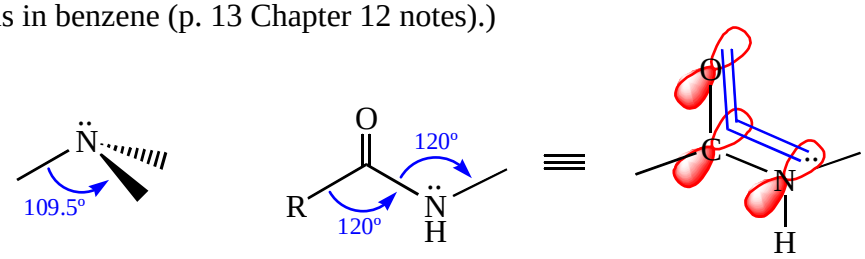
Just like the parent amino acids, peptides and proteins exist as zwitterions. And just like amino acids, proteins have isoelectric points. However, there is an important difference. While amino acids are not infinitely water soluble, under standard biological conditions they do not become insoluble. In general, as molecules become larger they become less soluble. Thus, all other things equal, proteins will be less soluble than the amino acids from which they are formed. You were told in Section 20.1 (p. 6) that the solubility decrease for amino acids at the pI was not of major significance, but it is for proteins. At the pI of a protein, its solubility is at a minimum and many proteins can precipitate from solution (become largely insoluble). This is why understanding pH is so important in the life sciences. If the pH of a biological solution (e.g. blood) strays too far from its normal value, proteins may begin to precipitate and this may cause cell or even organism death.

20.4 Secondary Structures of Proteins

Now that we have the sequence of amino acids that make up a protein, what does it tell us about the 3-dimensional molecular structure? On the surface, not much, but if we look deeper the information is there. To begin answering this question, let's look at the groups that make up the protein backbone. In particular pay attention to the atoms, bonds, and electrons highlighted in blue and green.



In CHM 203 you learned that the angles made by hydrogen around ammonia are approximately tetrahedral (~109.5º, p. 106 textbook), the same is true of organic amines. But the angles around amides are much closer to 120º than 109.5º. Why? In Chapter 12 (p. 4 notes) you learned that double bonds resulted from a standard single bond plus the side-to-side overlap of 2 *p*-orbitals. If, instead of placing the lone pair of electrons in an orbital like the ones it uses to bond to its neighbors, the electrons go into a *p*-orbital, that orbital can overlap the *p*-orbital on carbonyl carbon just like the *p*-orbital on the oxygen can. (This is very similar to the way bonding happens in benzene (p. 13 Chapter 12 notes).)



When this happens it is not possible for the molecule to twist around the C(O)-N bond like it can the C(substituent)-N bond. The result is that all of the atoms and bonds colored green lie in the same plane, as do all of the atoms and bonds in blue. Because each plane can rotate around the carbon(R") bond, these planes will rarely be parallel (coplanar). Because bond rotation can occur at only every third atom, this backbone is fairly rigid and this has important structural implications, as we shall soon see.

All peptides have many groups capable of hydrogen bonding. Each hydrogen bound to nitrogen can hydrogen bond to a carbonyl oxygen, either in an adjacent chain or if the backbone curls around on itself to a carbonyl oxygen further down the chain. Both kinds of associations occur. Thus, two out of every three backbone positions are (indirectly) available for hydrogen bonding.

The third position always carries a substituent. Whether the substituent can hydrogen bond

or not affects protein structure. Recall that substituents fall into one of two categories: polar or non-polar. All of the polar substituents can hydrogen bond, while none of the nonpolar substituents can. Without getting into detail here, peptide and protein strands will twist and/or align to group the nonpolar substituents together. An isolated nonpolar substituent can disrupt a sequence of twists. In short, switching between polar and nonpolar groups (and even different groups within a category because of different sizes and shapes) will disrupt coils and side-by-side associations. This contributes to the 3-dimensional structure of a protein.

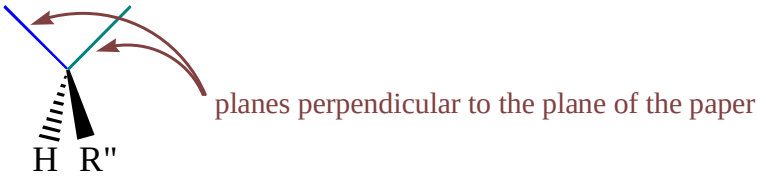
The two most common secondary structures are the α-helix and β-pleated sheet. We begin with the former. You have, of course, heard of the double helix associated with DNA and we will examine that in the final chapter. The shape of the α-helix is related to it. It takes 3.6 amino acid residues to complete a single turn of an α-helix. Thus, each amino acid residue hydrogen bonds to another amino acid residue 4 residues before and 4 residues after it in the coil. The length of one coil is about 54 nm (for comparison: one carbon atom diameter and a C-C single bond are each about 0.15 nm). The hydrogen bonds between the amide hydrogens and the carbonyl oxygens are parallel to the length of the coil. In an α-helix all substituent groups point outward. Your book shows an α-helix on p. 579.

As with all secondary structures, some R groups are poorly compatible with the α-helix. For example, glycine tends to make the coil too flexible (very small R), while proline tends to make it too rigid (including the amine N in the R group makes it too rigid). Likewise acid groups and large groups tend to disrupt the coils. This is not to say that these groups must be absent, only that they cannot appear frequently in an α-helix.

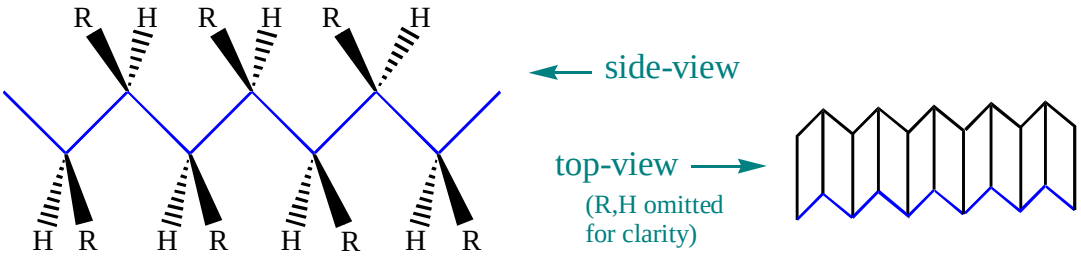
α-Keratin is a protein that makes up hair, nails, and hooves of most land animals. One of the distinctions of the particular α-keratin that makes up human hair is that the only secondary

structure that appears is the α-helix. It is important to remember that these secondary structures generally do not involve large numbers of amino acid residues. Your book tells us that 11 residues are common (roughly 3 full turns around the coil) and that 53 residues are the maximum (~14 turns). The point is that in any protein we can expect to see several different coils and/or other secondary structures present. Thus in the example of human hair, α-helices generally come in groups of 3. We shall soon see that this group of 3 helices makes up a tertiary structure. α-Keratin is discussed in more detail on pp. 20-21.

The second major secondary structure in proteins is the β-pleated sheet. Let's go back to the picture of the protein highlighted in blue and green on p. 8 of these notes. Looked at in the proper orientation, the planes intersect to form a V-shape. In the picture shown below, the blue and green lines represent the planes from the earlier structure.



If arranged properly, the following arrangement occurs:



where the blue zigzag line represents carbonyl/amide planes perpendicular to the plane of the paper. You might call this a "pleated strand." A pleated sheet arises when several pleated strands line up side-by-side and add depth to the structure. A pleated strand will incorporate 6 – 15 amino acid residues, while a sheet will be made of 2 – 15 pleated strands. β-Pleated sheets

are held together by hydrogen bonds just like α-helices.

You can make a similar structure with a sheet of paper by folding it at one-inch intervals accordion style. When unfolded you can see the origin of the name "pleated sheet." At each ridge maximum and minimum lies a pivoting carbon to which R and H bind. Along a top ridge these groups point up and along the ridge, while at the bottom they point down and along the ridge.

Flexible lengths of amino acid residues permit the strands to wrap around and align next to each other, connecting into pleated strands. The strands can either align in the same or opposite directions. In general, those with amino acid residues occurring in opposite sequences (proceeding in the opposite direction) are somewhat more stable than those with the same residues lined up side-by-side. Your book has a nice picture (Figure 20.6, p. 580) that shows how these two patterns of alignment can occur.

20.5 Tertiary Structures of Proteins

The actual 3-dimensional shape of an entire protein is its tertiary structure. Why make a fuss over this? After all, all molecules have a 3-dimensional shape, don't they? The answer to this question (as you have already guessed) is not usually. Some molecules, like benzene, have their atoms locked into place (e.g. by double bonds) and so have an enforced structure. Most molecules have many atoms with tetrahedral geometries that can rotate freely. For example, a molecule as simple as butane has two predominant rotational arrangements, while pentane has 4. In each case, the presence of multiple structures arises because there is free rotation about the C-C single bonds. Thus, in most molecules, there is no fixed shape.

As we have learned, proteins contain at least dozens of amino acid residues and each residue

contains (usually) two or more tetrahedral carbon. So why do these molecules have only one structure? When secondary structures form there are consequences beyond generation of that structural unit. For example, when an α-helix forms, the R groups bound to the tetrahedral (α) carbon point out from the spiral. If the R groups are hydrophobic water will bind poorly to it, causing the protein to coil in such a way as to keep water away from this region. If the groups are hydrophilic the protein may open up to allow water in or it may twist to increase intramolecular hydrogen bonding.

The point of this discussion is that each secondary structure affects the environment around it and the protein as a whole will rearrange to maximize interactions that stabilize it. This larger structure is held together in a number of ways. (1) Hydrophobic groups tend to cluster together. (2) Disulfide linkages form to provide the strength of covalent bonds between various structures. These bridges are generically called cross-links. (3) Ionic interactions between side chain ionic groups (CO_2^- and NH_3^+) provide ionic bonds between different regions of the protein backbone. These ionic interactions are sometimes called salt bridges. (4) Hydrogen bonding between amino acid residues.

Another tertiary structural feature warrants comment. Proteins frequently require the incorporation of one or more additional organic groups (that are not amino acid based) into their structures. These groups are called prosthetics and frequently are the groups that actually accomplish the function associated with that protein. Your book discusses the heme group in myoglobin. When the heme group (Figure 20.7b) includes an Fe^{2+} ion the protein acts as an oxygen storage unit. In hemoglobin this unit causes the protein to be an oxygen carrier. Some other examples include:

Protein	Prosthetic group	Function
casein	phosphate ester	milk protein
immunoglobulin	saccharide	antibody (5 different types: A, D, E, G, M)
RNA-bound protein	nucleic acid	protein synthesis in ribosomes (see Chapter 24)

20.6 Quaternary Structures of Proteins

Quaternary structures arise when two or more polypeptides (or proteins) assemble into a larger structure. In this structure they retain their separate identities. Each polypeptide is called a subunit. The subunits are held in place by the same 4 forces that operate in generating tertiary structures. You should read the discussion of collagen in your book as an example of a quaternary structure. We will see in the next section the consequences of altering a protein's shape and how easy it is to do so. Hemoglobin is a quaternary structure consisting of 4 different proteins.

20.7 Common Properties of Proteins

As you have seen, proteins carry out a wide variety of functions in the body. It is interesting that, despite this, proteins behave in chemically similar ways. This is because they are composed of similar (perhaps the same) amino acid residues and are strung together using the same peptide linkages.

The most severe thing that can be done to a protein is hydrolysis (occurring as digestion). In this process your body releases enzymes into the digestive tract that break the peptide bonds to form individual amino acids. These are then absorbed into the body for reassembly into proteins it can use. In a similar way, enzymes in your body can break proteins down into amino acids for

repair of damaged proteins or conversion of one protein into another.

Under ordinary conditions, the damage to a protein is most likely to occur through denaturing. Denaturing is the disruption of the shape (organization) of a protein in its naturally occurring state (called the *native protein*). Generally speaking disrupting any significant part of the secondary, tertiary, or quaternary shape may result in protein denaturation. Denaturing a protein is bad because it renders the protein inactive (at best). What's worse is that under normal biological conditions denaturation is not routinely reversible.

Many things will denature a protein, although only a few of them are problems under normal biological conditions. Table 20.2 lists the major ways to denature a protein. Of these heat (as in frying, boiling, microwave radiation), violent mechanical agitation, soaps, and the addition of organic solvents do not normally occur in living beings. (And as any lobster will tell you, protein denaturation is the least of its problems when dropped into boiling water.) The other problems: UV radiation, adding "strong" acids/bases, adding heavy metal ions, and altering the ionic concentration of the bodily fluid (not listed in your book) are all problems that can occur in real living systems. Let's examine them individually.

UV radiation is only a problem near your body's skin. UV light can penetrate the skin and can (conceivably) denature proteins in cells at or very near the surface of your body. The power of UV radiation to affect molecules is demonstrated by causing both suntans and sunburns in the short term, and it can lead to skin cancer over the long term. Exposure to UV light also causes cataracts.

While strong acids and bases are not normally a problem for people or animals, managing the pH of your bodily fluids is of utmost importance. For example, your blood has a slightly basic pH (7.35) and changes of more than 0.2 – 0.3 units from that value can be fatal. Since your

bloodstream is a closed system (under non-bleeding conditions) it might seem as if this were a minor point. Not so. A waste product of energy production is carbon dioxide, CO_2, and you may recall from CHM 203 (Chapter 8, p. 211) that it reacts with water to form carbonic acid, H_2CO_3.

$$CO_{2\,(g)} + H_2O_{(\ell)} \rightleftharpoons H_2CO_{3\,(aq)}$$

The pH of a saturated carbonic acid solution is about 3.8, far lower than that of blood. The result of a failure of the body's system of removing CO_2 would be the rapid lowering of blood pH and the concomitant denaturing of blood borne proteins. Shortly thereafter death would likely result. (That this is valid may be shown by CO_2 fire extinguishing systems. In remote (unmanned) chemical storehouses, automatic CO_2 fire extinguishers work by rapidly (< 30 seconds) replacing all of the air with CO_2. Within a minute (even if one tries to hold one's breath) unconsciousness and death follow CO_2 release.)

Another way to denature proteins is by heavy metal poisoning. Metal ions, generally from the second and third transition series (e.g. Pb^{2+}, Hg^{2+}, Cd^{2+}), tend to bind strongly to the sulfur atoms in cysteine. These links either result in the protein precipitating from solution or the generation of multiple metal-S links that alter the protein configuration.

The final, real world way you can denature your proteins is by altering the ionic balance of bodily fluids. This is similar to pH changes in that a crucial regulatory system in your body must break down. Denaturing occurs here because the change in ionic balance changes ionic bonding between amino acid residues and alters patterns of hydrogen bonding. Each results in a modified protein 3-dimensional geometry.

The devastating effects caused by only a small amount of altered proteins is demonstrated by prions. Prions are a class of infectious agents that has only recently been recognized (1982,

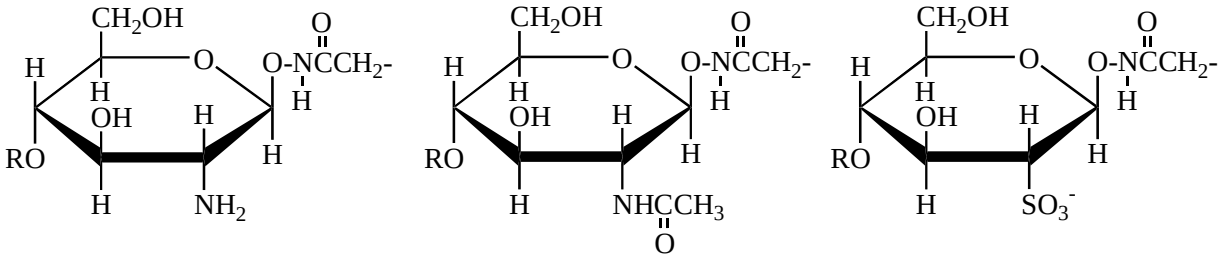
Dr. Stanley Prusiner, Univ. of Calif. School of Medicine at San Francisco). The word prion is derived from the phrase 'proteinaceous infectious particle'. It is different from all other infecting agents because it has no nuclear material (of the biological type). It appears that prions work by infecting a cell and inducing other proteins to alter their shapes. Once altered the protein ceases to perform its normal function and may engage in harmful activity. Several diseases are now recognized as originating from a prion infection. They include Creutzfeldt-Jakob disease, kuru, Gerstmann-Sträussler-Scheinker disease, and the so-called “mad cow disease.” Each exhibits very similar symptoms. Both kuru and mad cow disease have been established as resulting from the consumption of contaminated meat (human and beef, respectively). Creutzfeldt-Jakob disease has been accidentally transmitted by corneal transplants and human growth hormone therapy.

As stated in Section 20.3, changing the pH of a solution to the pI of a protein will result in its precipitation. Thus even if the pH change doesn’t denature a particular protein; it may be removed from solution. The result is essentially the same thing as denaturing, the absence of a protein that is necessary for life functions.

20.8 Cell Membranes Revisited – Glycoprotein Components

In Chapter 19 we learned that cell membranes were made up mostly of lipids (fatty acids and steroids), but also had protein components that allow material to be transported into and out of the cell. All cell membrane proteins are glycoproteins. That is, all of these proteins contain a sugar molecule (oligosaccharide), as a prosthetic group. As you might expect the sugar joins to the protein through the acetal –OH group. It always joins to the protein at the terminal ammonium position (instead of the $-CO_2^-$ terminus). Furthermore, the number 2 carbon is

always substituted either with an amine, amide, or sulfate group. Representative examples include:



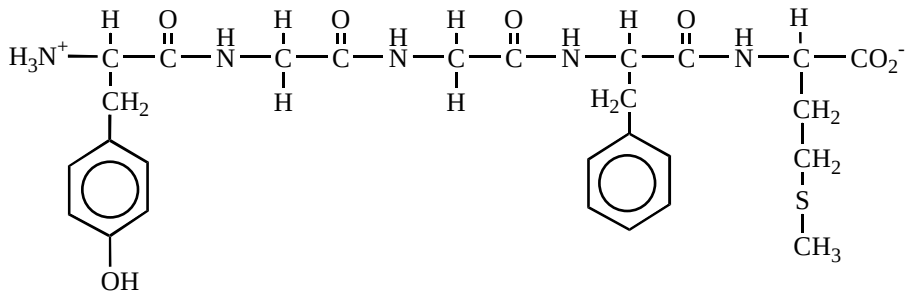
When a substance is added to a normal fluid (e.g. water), there are regions of high concentration and zero concentration at the beginning, but over time the concentration of the substance becomes equal everywhere. Consider a cup of hot water. If you dunk a tea bag in it, there will be a brown splotch where the bag went in and out. Even if you don't stir the tea, after a while the water will develop a uniform light brown color as the tea diffuses through the cup. In nature, the equalizing of such concentration gradients occurs spontaneously (i.e. without outside intervention).

In cells this natural diffusion is deadly. We have larger concentrations of some ions in our cells than outside (e.g. in blood) and lower concentrations of others. For the cell to function properly, it must have a system whereby the proper concentrations of all ions are maintained (i.e. sustaining a concentration gradient). One such concentration gradient in the body relates to sodium (Na^+) and potassium (K^+) ions. Your body maintains a higher concentration of sodium ions in the blood than in cells. The reverse is true of potassium ions. This protein complex (called the sodium-potassium pump) moves potassium ions into cells and sodium ions out of them to maintain the proper balance. Proteins of this type were described briefly in the last chapter.

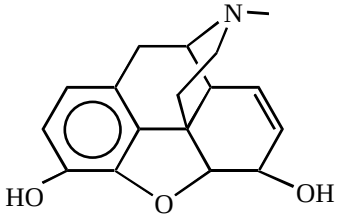
Another type of protein extends from the interior of one cell through its membrane and the membrane of a neighboring cell into the second cell's interior. This type of protein is called a

gap junction and it allows the transport of materials from one cell directly to another. These proteins are necessary because not all cells are directly adjacent to blood vessels and a means of supplying nutrients and removing waste products is necessary. Your book discusses these molecules in some greater detail.

A third type of protein acts as a receptor for molecules outside the cell. The receptor binds molecules with only a very specific shape (e.g. hormones). The binding alters the protein in such a way as to cause the part inside the cell to generate a physiological change. One example of such a protein is the one that binds insulin. On binding insulin, the protein initiates a series of changes that result in the cell bringing in glucose. Some receptors in the brain bind enkephalins, molecules which, on binding, appear to block pain sensation. Heroin and morphine activate these receptors. All along, we have been telling you that proteins bind only a certain shape. Drugs and diseases sometimes work by mimicking that shape. You would think (or at least I would) that the part involved in binding would have to be essentially identical to the natural binding agent. Differences could occur further away, but not really close to the binding site. If you assumed this, you too would be wrong. Below are the structures of methionine enkaphalin and morphine, both activate the same protein. Apparently the pocket fits morphine and heroin just right. Heroin looks just like morphine except the –OH groups are replaced by $-OC(O)CH_3$ groups.



methionine enkephalin (try-gly-gly-phe-met)



morphine

The primary difference between morphine (and heroin) and enkephalins is that when the latter binds to a receptors cell the body rapidly sends an enzyme to hydrolyze the polypeptide so that its effect is short lived. The body has no way to break-up a morphine or heroin molecule so their effects last much longer. Without going into detail, the addiction associated with these drugs is caused by the long-term attachment of the drug to the receptor. This causes a prolonged suppression of a compound that tells the body there is pain somewhere. Increasing dosages increase the suppression. When the drug is removed, the cells in the body enter a hyper mode producing this pain indicating compound to get levels up to where they should be. Unfortunately, the body has gets accustomed to the lower level and then it reacts as if there is pain everywhere. This is commonly called withdrawal.

20.9 Classes of Proteins

Two ways proteins may be classified are by solubility and function. Within the solubility category there are subcategories that describe either a second physical property or a function.

Fibrous proteins are water insoluble. They include the collagens, elastins, keratins, myosins, and fibrin. Globular proteins are water-soluble and include the globulins and albumins. The name of each category tells you something important about each classes physical shape. Two globular proteins are hemoglobin and myoglobin. The latter is discussed briefly in your book.

One fibrous protein is α-keratin (there are two types). Each protein molecule is an extended α-helix because it employs no amino acids that disrupt the formation of α-helices. Furthermore, because it projects all of its hydrophobic groups outward, its quaternary structure is that of a pair of intertwined α-helices (a double helix). A hair is composed of a collection of these pairs

coiling around one another in a superhelix. The helices within the superhelix are held together by hydrogen bonding and disulfide bridges. The way the hair treatment called a “perm” works is the hair is first treated with a reducing agent to break the disulfide bonds, then it is curled into the desired shape, then an oxidant is added to reestablish the disulfide bonds. The treated hair is thereby held permanently in the determined shape. The perm is lost because the treatment doesn’t alter how the hair is grown.

Collagen (20 types) has a similar structure to keratin except that it exists as a triple helix. This is the most abundant protein found in vertebrate animals and is found in teeth, nails, bone, skin, and tendons. In teeth and bones the collagen is strengthened by the incorporation of inorganic materials such as hydroxyapatite polymer ($[Ca_5(PO_4)_3(OH)]_x$). Collagen is discussed in your book on p. 583 in some detail.

Nine categories of protein functionality are enzymes, contractile tissue, hormones, neurotransmitters, toxins, and storage, transport, structural, and protective proteins. Examples of each are provided in the book on pp. 596-597.

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