

Protein Structure¹

Model 1. At its simplest level, protein structure is a chain of amino acid residues joined by *peptide bonds*². We can think of a protein chain as a *peptide backbone* from which project the different side chains of the amino acid residues. In Figure 6.1 below, the *peptide backbone* is shown in blue.

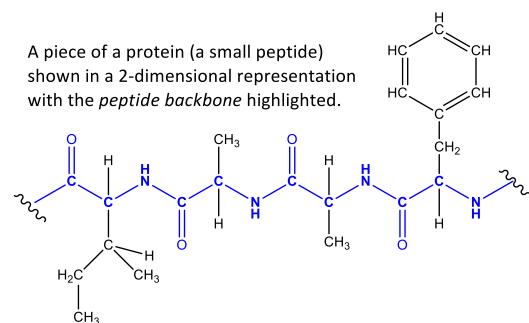


Figure 6.1. A region of protein sequence. The peptide backbone is shown in blue. The side chains of (L > R) isoleucine, alanine, alanine and phenylalanine are in black.

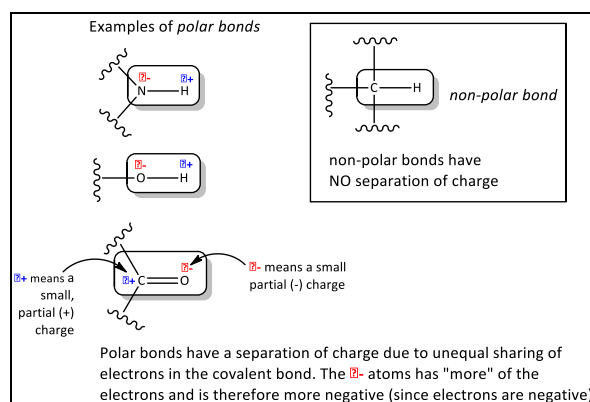
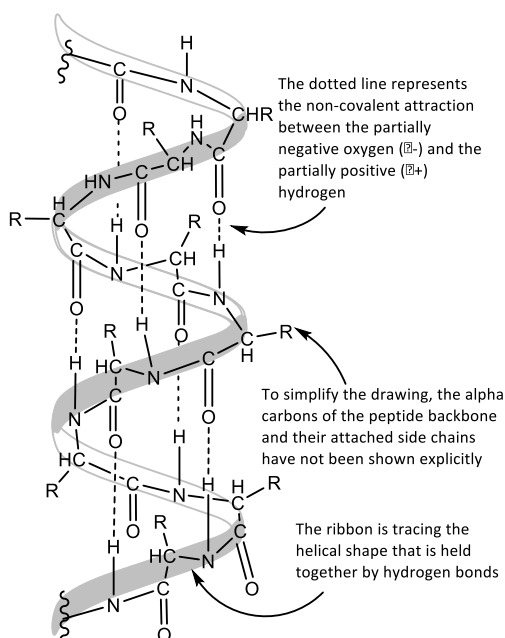


Figure 6.2. Examples of polar and non-polar bonds

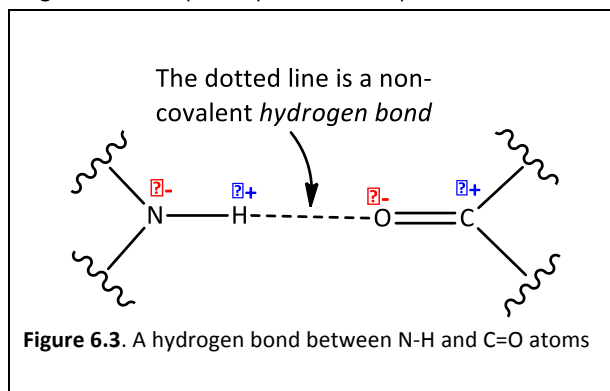
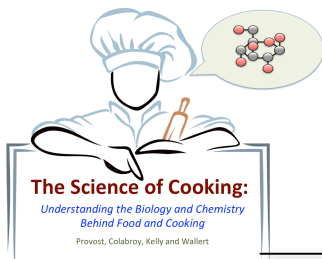


Figure 6.4. The N-H and C=O bonds of the *peptide backbone* engaging in non-covalent hydrogen bonds.

¹ At the discretion of the instructor, this activity could accompany the activities on Eggs and/or Meats.

² For a lesson on amino acids and peptide bonds see Activity 5



Proteins also contain *polar* and *non-polar* bonds. When two atoms are joined by a polar bond, one of the atoms has a partially negative (δ^-) charge, while the other atom has a partially positive (δ^+) charge. The charge comes from an unequal sharing of the electrons in the conjoining covalent bond. These partially charged atoms can form *weak, non-covalent* attractions that hold the two atoms near one another in physical space. If the *weak, non-covalent* attractions involve a partially positive (δ^+) hydrogen atom – then the attraction is called a *hydrogen bond*.

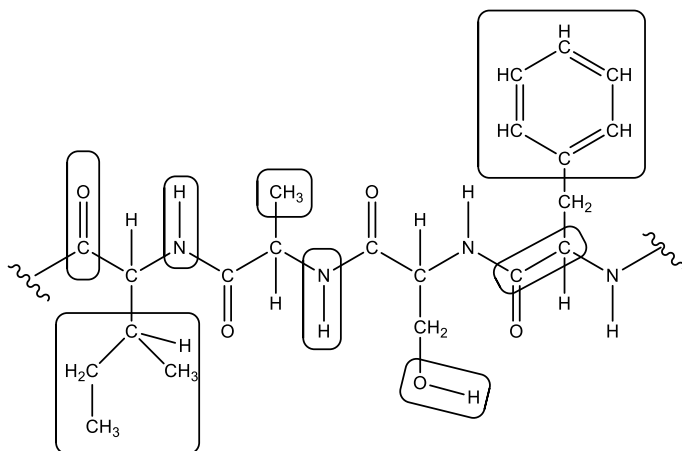
In proteins, the N—H and C=O bonds of the peptide backbone can form *hydrogen bonds* with one another. These hydrogen bonds can stabilize 3-dimensional arrangements of amino acids residues in what is called *secondary structure*. Figure 3 is an example of *secondary structure* called an *alpha (α) helix*. The *primary sequence*³ of amino acids determines whether or not it will fold into an α -helix or another type of *secondary structure*.

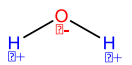
Questions:

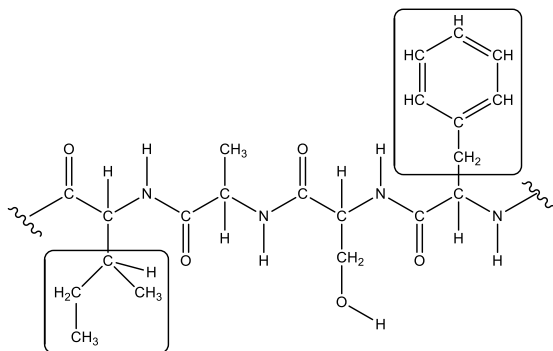
1. Why can hydrogen bonds form between the N—H and the C=O of the peptide backbone but not between the alpha carbon and its hydrogen (C—H)?
2. Draw in the partial negative (δ^-) and partial positive (δ^+) charges on the atoms of Figure 3 that are engaged in *hydrogen bonding*.

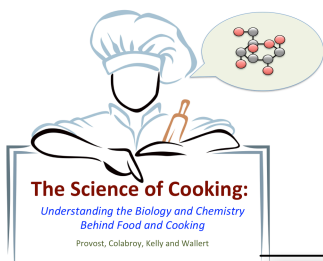
³ See Activity 5 for a lesson on primary sequence

3. Shown below is a drawing of a peptide. Label each box as containing polar or non-polar bond(s).



4. Water is another molecule with polar bonds (O—H) .
- Using the structure below, show how water would interact through at least three different *non-covalent hydrogen bonds* with the peptide. Draw in the partial negative (δ^-) and partial positive (δ^+) charges. These parts of the structure are called *hydrophilic* (literally, “loves water”)
 - Explain why the areas of the structure that are boxed are called *hydrophobic* (literally, “fears water”) – these areas of the structure do *not* interact with water. Why?





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Model 2. Proteins are *amphiphilic* molecules - they have both *polar* (*hydrophilic* = “loves water”) and non-polar (*hydrophobic* = “fears water”) parts. In nature, we find proteins in water based environments. Because not all parts of the protein love the water (some parts are *hydrophobic*) the protein *folds* in a 3-dimensional way that buries the *hydrophobic* parts on the inside of the structure, and exposes the *hydrophilic* parts to the outside, where they can interact with the watery environment.

Key Concept

Most proteins fold into 3-dimensional structures made of α -helices, β -sheets and loops each held together by hydrogen bonds. The protein folds in order to hide hydrophobic parts and expose hydrophilic parts to water.

Modern biochemistry has allowed scientists to “see” how proteins fold at a molecular level. What they found was quite beautiful (see Figure 6.5).

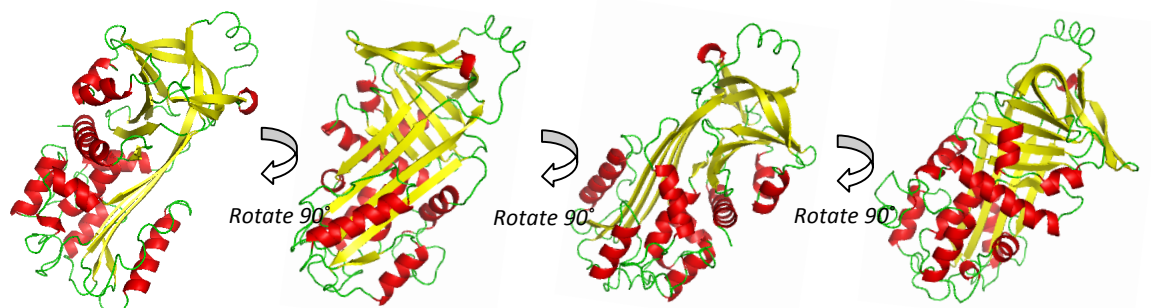


Figure 6.5. The protein ovalbumin (from chicken egg white) as viewed rotating around a vertical axis⁴.

But how can Figure 6.5 be depicting a protein? There are no visible amino acids or peptide bonds, just twirly ribbons and curvy arrows. What are these images depicting anyway?

From Figures 6.5 and 6.6, we can see that the protein ovalbumin has many α -helices and β -sheets all *folded* on top of and around each other to make a *globular* structure. In fact, when you fill in all the atoms using a type of *space filling* representation, we can see the lumpy, 3-dimensional *globular* looking protein (Figure 6.7). The α -helices, β -sheets and loops also interact *with each other* by hydrogen bonds.

⁴ Images of ovalbumin in Figures 6.5-6.9 were author-generated using PDB: 1UHG (J.Biol.Chem.(2003) **278**: 35524-35530) and PyMol.

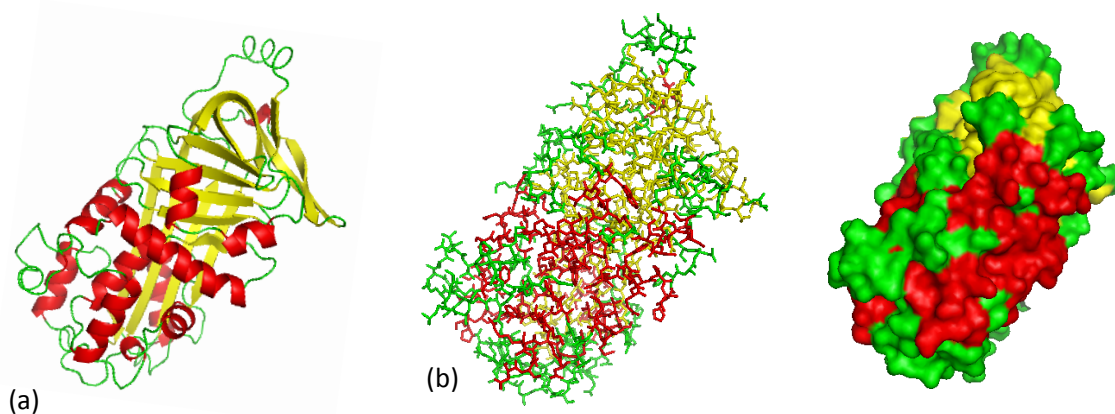
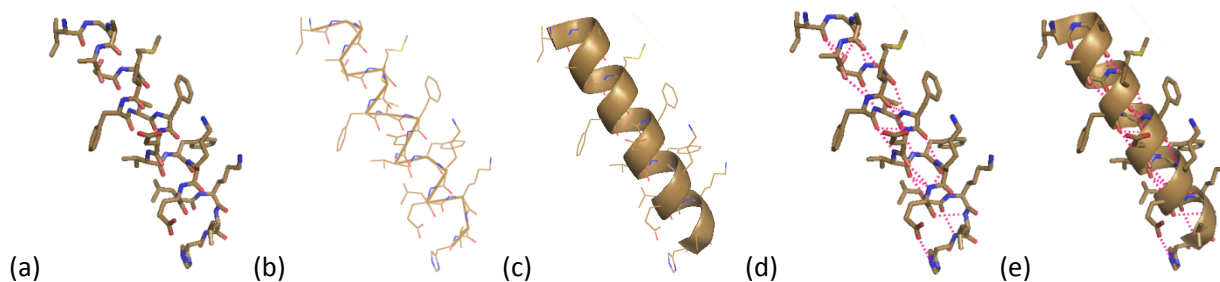
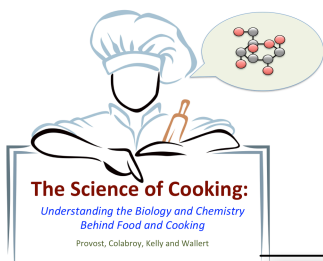


Figure 6.6. The same orientation of the ovalbumin protein molecule represented as a cartoon (a), and then as using *amino acid residues* (b) – the amino acids joined by peptide bonds.

Figure 6.7. A *space filling* representation of ovalbumin. Red are α -helices, yellow are β -sheets and green are loops



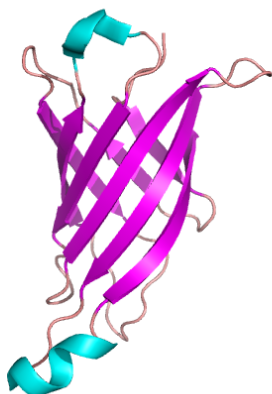
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6. Why do proteins fold into 3-dimensional globular structures made of α -helices, β -sheets and loops? Use the words *polar* and *non-polar* in your answer.

7. Shown below is the structure of the protein avidin – also found in chicken egg white.

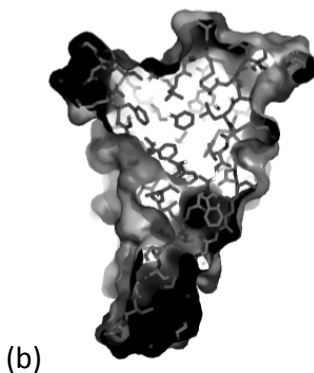
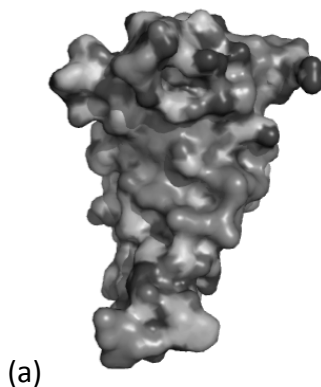


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c. Using arrows, identify an α -helix and a β -sheet (a β -sheet is comprised of 2 or more β -strands).

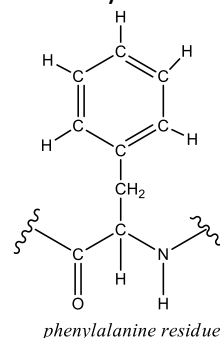
d. What type of secondary structure do you find in avidin *most* often?

8. There are two representations of avidin below. The first (a) shows the overall globular protein in a “space filling” model. The second (b) is a slice right through the middle of avidin – so we can see what the protein looks like on the inside.



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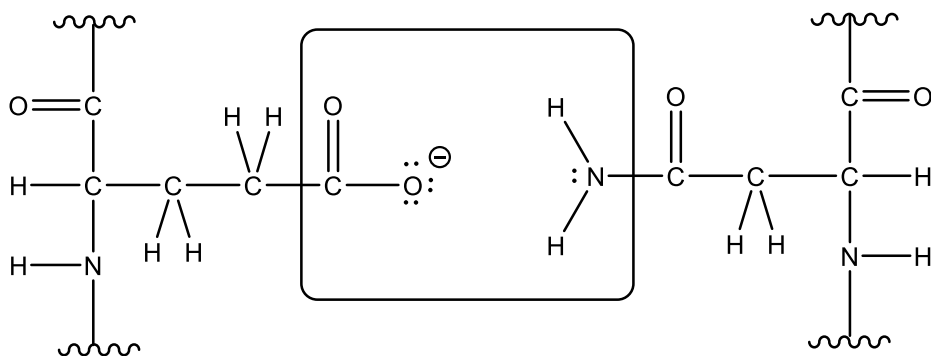
On the interior of avidin, we find several phenylalanine residues. Why?



⁵ This image was author-generated from the PDB: 1VYO (Chem.Biol. 2006 **13**: 1029) using PyMol.

⁶ These images were author-generated from the PDB: 1VYO (Chem.Biol. 2006 **13**: 1029) using PyMol.

9. 3-dimensional protein structure can also be held together by interactions of ionic⁷ amino acid side chains. Drawn below are two amino acid side chains – a glutamate and an asparagine. The glutamate is an anion. For the bonds inside the “box”, draw in partial positive ($\delta+$) and negative ($\delta-$) charges, then use dotted lines to show any non-covalent attractions between the glutamate and asparagine atoms in the “box.”



⁷ In this example, the glutamate has an anionic oxygen (negatively charged). The presence of the full charge means this oxygen is *ionic* – rather than *polar*.

Protein structure...unraveled

Model 3. There is more than one way to disrupt unfold or otherwise ruin the *folded* protein structure. Unfolding of a protein is called *denaturation*. *Denaturation* is the process of disrupting the *hydrogen bonds* and other non-covalent interactions holding the pretty α -helices, β -sheets and loops together, and the 3-dimensional *globular* protein structure unravels. When the protein unfolds, all the *hydrophobic* parts that were buried inside the protein are exposed to the watery environment – AH! The hydrophobic parts *hate* the water, and instead they'd like to find another hydrophobic place to be. The exposed hydrophobic parts of a protein join together with exposed hydrophobic parts of other proteins, clumping together in a process called *coagulation*. The *unfolded, coagulated* protein is now a large, aggregated complex that can't stay dissolved in the water – so, the coagulated protein *solidifies*, trapping other molecules (such as water or fat) between the unfolded proteins.

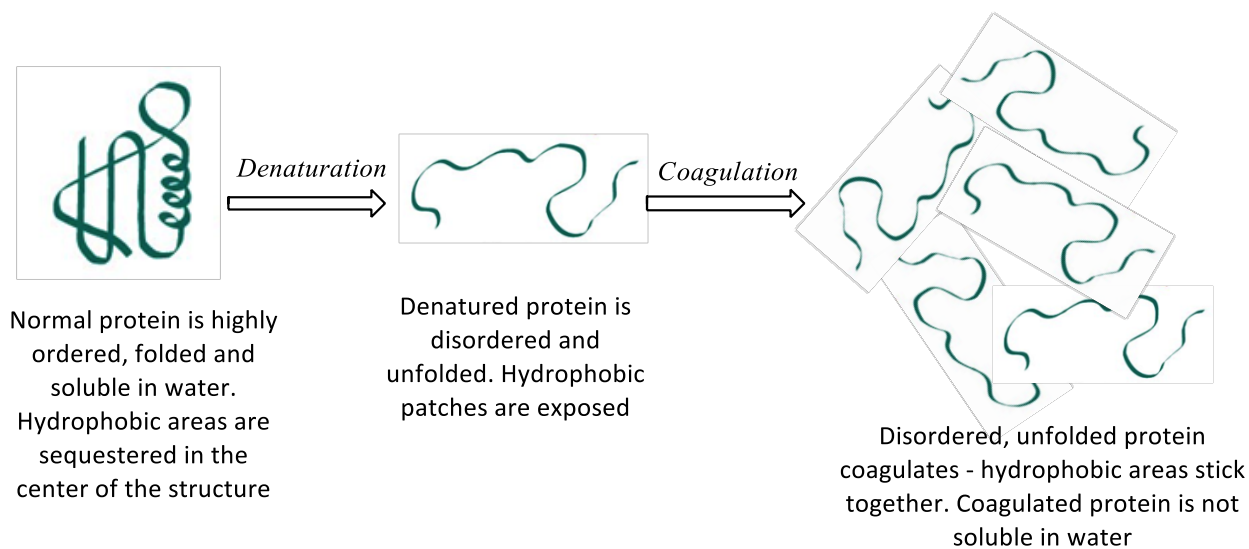


Figure 6.10. Protein Denaturation and coagulation at the molecular level⁸

Heat is one strategy for protein denaturation. When a protein is *denatured* by heat, the heat energy added to the mixture of proteins makes the molecules move around. Add enough energy and the proteins move and groove enough to break all the *non-covalent*

⁸ The cartoon images are from Boyer's Concepts in Biochemistry, 3rd edition, p.110, Figure 4.6

interactions holding the protein together, and the 3-dimensional *globular* protein structure unravels. This is the type of denaturation and coagulation we see in the cooking of an egg.

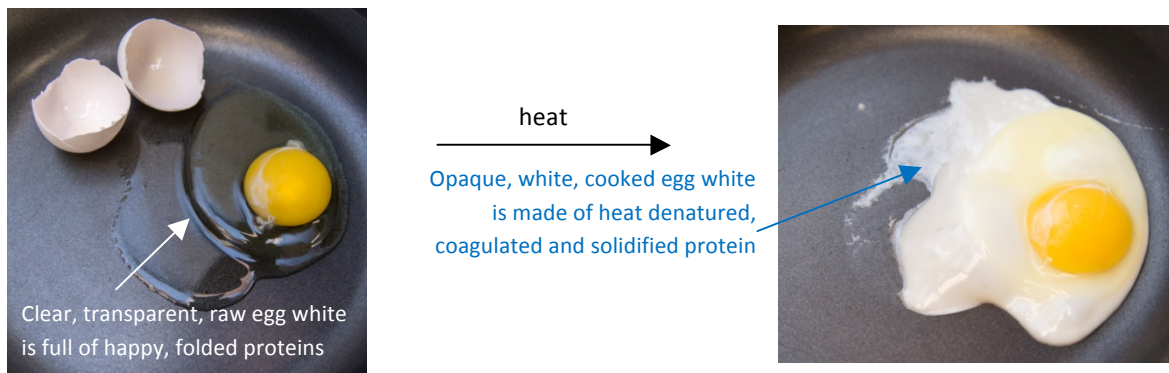


Figure 6.11. Protein denaturation and coagulation caused by heat – as seen with the unaided eye. *Photos by Bill Keller*

Acidic conditions are another way to *denature* protein. Some amino acid side chains react with the protons (H^+) in acid. Amino acid residues like lysine, aspartate or glutamate have side chains that gain or lose a proton (H^+) depending on the pH– these atoms are said to be *protonated* (gain of H^+) or *de-protonated* (loss of H^+).⁹ Changing the charge disrupts non-covalent interactions between amino acid residues.

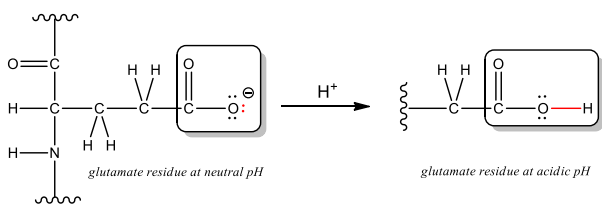
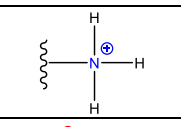
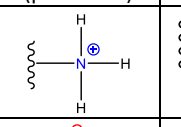
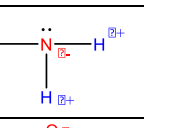
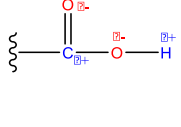
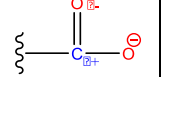
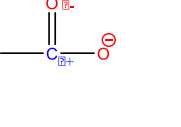
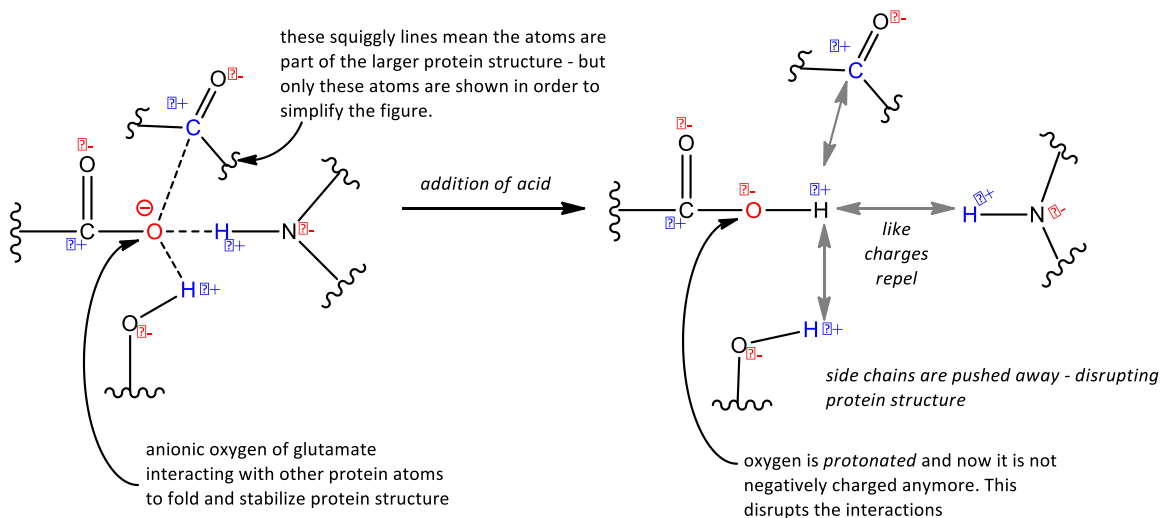


Figure 6.12. The side chain of the amino acid residue glutamate after *protonation* under acidic conditions.

Table 6.1. Amino acid side chains and pH

Very Acidic ($< \text{pH } 4.5$)	Mildly acidic to mildly alkaline ($\text{pH } 4.5\text{--}10$)	Very alkaline ($\text{pH } > 10$)
		
		

⁹ For a lesson on pH, acids, protonation and deprotonation – see Activity 8.



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